



PHD

N-Oxides as Organocatalysts for the Baeyer-Villiger Oxidation and Bromination Reactions

Lawrence, Ruth

Award date:
2017

Awarding institution:
University of Bath

[Link to publication](#)

Alternative formats

If you require this document in an alternative format, please contact:
openaccess@bath.ac.uk

Copyright of this thesis rests with the author. Access is subject to the above licence, if given. If no licence is specified above, original content in this thesis is licensed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International (CC BY-NC-ND 4.0) Licence (<https://creativecommons.org/licenses/by-nc-nd/4.0/>). Any third-party copyright material present remains the property of its respective owner(s) and is licensed under its existing terms.

Take down policy

If you consider content within Bath's Research Portal to be in breach of UK law, please contact: openaccess@bath.ac.uk with the details. Your claim will be investigated and, where appropriate, the item will be removed from public view as soon as possible.



***N*-Oxides as Organocatalysts for the Baeyer-Villiger Oxidation and Bromination Reactions**

Ruth Lawrence

A thesis submitted for the degree of Doctor of Philosophy

University of Bath

Department of Chemistry

September 2016

COPYRIGHT

Attention is drawn to the fact that copyright of this thesis rests with the author. A copy of this thesis has been supplied on condition that anyone who consults it is understood to recognise that its copyright rests with the author and that they must not copy it or use material from it except as permitted by law or with the consent of the author.

This thesis may be made available for consultation within the University Library and may be photocopied or lent to other libraries for the purposes of consultation with effect from.....

Signed on behalf of the Faculty of Science.....

Abstract

This thesis is concerned with exploring novel applications of *N*-oxides as organocatalysts. Specifically, aromatic *N*-oxides have been successfully implemented as catalysts within the Baeyer-Villiger oxidation of α,β -unsaturated ketones and electrophilic aromatic bromination reactions.

Chapter 1 provides a review of the current applications of *N*-oxides, highlighting their use as organic oxidants, neutral ligands and in particular organocatalysts. These roles exploit several key features of the *N*-oxide, including the intrinsic weakness and polarity of the N→O bond, their Lewis basicity and ability to function as hydrogen bond acceptors. As organocatalysts, these species have predominantly been utilised as nucleophilic catalysts, however their potential to act as hydrogen bond catalysts represents an emerging area of interest.

Chapter 2 describes the development of an organocatalysed Baeyer-Villiger oxidation, for which *N*-oxides and carboxylates have been identified as suitable catalysts. The optimised protocol, which employs DMAP as the pre-catalyst, was applied to a wide range of saturated and more specifically α,β -unsaturated ketones, with enhanced reaction rates and/or chemoselectivities achieved in the majority of cases. From extensive mechanistic studies, it is proposed that the *N*-oxide functions as a hydrogen bond acceptor; facilitating concerted proton transfer within the addition step. The unique role of the catalyst allowed for predictions to be made about the rate determining step of the oxidations performed. A series of by-products obtained from the over-oxidation of (*E*)-4-phenyl-3-buten-2-one were characterised and the mechanistic pathway for their formation has been fully elucidated. Development of the reaction conditions for the selective formation of many of these species is also provided. Additionally, the novel reactions of 3-(4-methoxyphenyl)but-3-en-2-one are examined.

Chapter 3 details investigations into the applicability of the novel, relatively bench stable formate ester, (formyloxy)(phenyl)methyl acetate, as a formylating reagent. A high yielding and operationally simple procedure for the synthesis of this formate ester from commercially available, inexpensive (*E*)-4-phenyl-3-buten-2-one is described in Chapter 2. A solvent and catalyst free protocol has been developed for the *N*-formylation of various amino species including primary and secondary (aliphatic and aromatic) amines and an amino acid ester as well as the *O*-formylation of alcohols. Demonstrating its synthetic utility, the developed methodology was applied to the one-pot synthesis of an isocyanide from the corresponding amine as well as the *N*-formylation of an unprotected amino acid under aqueous conditions.

Chapter 4 outlines preliminary studies into the application of *N*-oxides as nucleophilic catalysts for electrophilic aromatic bromination reactions with elemental bromine. The development of novel methodology for the 4-picoline *N*-oxide catalysed regioselective monobromination of *tert*-butylbenzene is discussed, for which a reactive *N*-oxide bromine complex is thought to be generated *in situ*. Conditions have also been established for a KI promoted system, with IBr proposed as the catalytic species. Both methodologies allow for selective electrophilic aromatic bromination of toluene in the light without competitive benzylic bromination.

Chapter 5 contains experimental procedures and compound characterisation data for Chapters 2-4 inclusive.

Acknowledgements

First and foremost I would like to thank Professor Steve Bull and Professor Jonathan Williams for encouraging me to pursue a PhD and for giving me the opportunity to work in their research groups; it really has been an invaluable experience. I truly appreciate all of their guidance and support over the past few years and for their continual enthusiasm and patience, despite my many questions and unknowns. I would also like to thank them for providing me with the opportunity to attend conferences, work on projects unrelated to my own and be involved with tutoring. I was lucky enough to be awarded funding from the University of Bath and for this I am extremely grateful.

I would also like to thank those who provided expert analytical support. Specifically, Dr John Lowe for all of his NMR assistance and for always taking the time to answer any queries in detail. Also, Dr Anneke Lubben for her patience running my many problematic mass spec samples and Dr Mary Mahon for obtaining crucial X-ray crystallographic data. For his helpful suggestions and insight into the Baeyer-Villiger oxidation mechanism, I would like to thank Dr Antoine Buchard.

During my PhD, I have had the opportunity to supervise some exceptional project students: Robert Chapman, Bill Cunningham and Caroline Jones; many of whose work features within this thesis. I would like to thank each one of them for their hard work and contribution. Thanks also to Robert Chapman for continuing the work presented in Chapter 3. Additionally, I would like to acknowledge Dr Marc Hutchby for the synthesis of some of the starting materials in Chapter 2, which greatly aided progress.

For their help proof reading this thesis, I would like to thank Prof. Steve Bull, Dr Rosie Chhatwal and Dr Samuel Cosham. Also, thanks to everyone who took an interest in my work and spent time brainstorming ideas.

A big thank you must also go to all of the Bull and Williams group members both past and present, who have not only taught me so much but have also been great fun to work with. To Dr James Taylor, Dr Lucy Peacock, Dr Jen Peed, Dr Rob Archer, Dr Caroline Evans and Dr Paul Fordred - thank you all for welcoming me into the group, helping me find my feet and for your great advice. Also to Dr Sarah Abou-Shehada, Dr Rosie Chhatwal, Dr Ben Atkinson, Dr Richard Blackburn, Dr Luke Williams, Rob Chapman, Caroline Jones, Dr Emily Border, Dr Dave Tickell, Bill Cunningham, Dr Marc Hutchby, Emma Lampard and Amy Groome thank you for your friendship, support, the many laughs and for contributing to some amazing memories over the past few years. It really has been great working with you all!

To my partner Sam, thank you for always believing in me, being there for me and reassuring me. Without your love, support and guidance I wouldn't be where I am today. Thanks must also go to my incredible family. To my Mum and Dad for their love, encouragement and support in everything I do. Thank you for always being there for me and for believing in me. In particular I would like to thank my mum for always being on the other end of the phone for a chat. Thanks to my sister, Emma, for being an amazing friend, for always taking an interest in what I am doing and for organising some great weekends. Lastly but by no means least I would like to thank the newest addition to my family, Jake (Jakey Woo). Thank you for all of the wonderful lunch parties and for always making me laugh – you made writing up so much more fun!

Declaration of material from a previously submitted thesis and of work done in conjunction with others

Chapter 2:

- Preliminary investigations into the Baeyer-Villiger oxidation had previously been undertaken by Dr Iwan Davies, Dr Paul Fordred and Amandine Altmayer-Henzien and identification of the ability of *N*-oxides to catalyse the reaction was established.
- Optimisation studies, isolation/identification of by-products (**338**, **339**, **341** and **342**), initial examination of the substrate scope and mechanistic studies were performed in conjunction with Robert Chapman (MChem student, October 2011-April 2012).
- The adapted procedure for the large scale synthesis of formate ester **354** was developed by Robert Chapman.
- Dr Marc Hutchby was responsible for the synthesis and isolation of the α,β -unsaturated ketones in Table 15 prepared by method A, ketones **413** and **485**, as well as for the purification of **407** and **408**.
- Crude 4-aminopyridines **361** and **362** were prepared by Dr Sarah Abou-Shehada

Chapter 4:

- The optimisation studies for *N*-oxide catalysed bromination reactions outlined in Chapter 4 were performed in conjunction with Caroline Jones (MRes student, June 2013-September 2013)

Abbreviations

Analytical

CI	Chemical ionisation
<i>c</i>	Concentration
<i>d</i>	Deuterated
<i>de</i>	Diastereomeric excess
d.r.	Diastereomeric ratio
<i>ee</i>	Enantiomeric excess
ESI	Electrospray ionisation
FTIR	Fourier transform infrared
GC	Gas chromatography
GCMS	Gas chromatography mass spectrometry
HRMS	High resolution mass spectrometry
h ν	Light
IR	Infrared
<i>J</i>	Coupling constant
LC	Liquid chromatography
mp	Melting point
MSD	Mass selective detector
MW	Microwave
<i>m/z</i>	Mass-to-charge ratio
nESI	Nanoelectrospray ionisation
NMR	Nuclear Magnetic Resonance
TLC	Thin layer chromatography
TOF	Time of flight
<i>t_R</i>	Retention time
UV	Ultraviolet
δ	NMR chemical shift
{ ¹ H}	Proton decoupled
[α] _D	Specific rotation
λ	Wavelength
ν	Wavenumber
app.	Apparent
br.	Broad

d	Doublet
dd	Doublet of doublets
ddd	Doublet of doublet of doublets
dt	Doublet of triplets
m	Multiplet
(M)	Major
(m)	Minor
q	Quartet
sept.	Septet
sept.d	Septet of doublets
s	Singlet
t	Triplet
td	Triplet of doublets
tt	Triplet of triplets

Units

cm	Centimetre
d	Days
dm	Decimetre
equiv. / eq	Equivalents
g	Gram
h	Hour
Hz	Hertz
K	Kelvin
m	Metre
M	Molar concentration (mol dm^{-3})
mg	Milligram
MHz	Megahertz
min	Minute
mL	Millilitre
mm	Millimetre
mmol	Millimole
mol%	Mole percentage
N	Normality
nm	Nanometre
ppm	Parts per million

w/w	Weight/weight
wt%	Weight %
v/vol	Volume
Å	Angstrom
°	Degree
°C	Degrees celcius
μL	Microlitre
μm	Micrometre

General terms

aq.	Aqueous
Cat.	Catalyst
COPD	Chronic obstructive pulmonary disease
EDG	Electron donating group
EWG	Electron withdrawing group
<i>i</i>	<i>iso</i>
KIE	Kinetic isotope effect
L	Generic ligand
LA	Lewis acid
LB	Lewis base
LG	Leaving group
lit.	Literature
<i>m</i>	<i>meta</i>
M	Metal
MBH	Morita-Baylis-Hillman
n.d.	Not determined
Nuc	Nucleophile
<i>o</i>	<i>ortho</i>
[O]	Oxidant
<i>p</i>	<i>para</i>
RDS	Rate determining step
R ^M	Migrating group
ROP	Ring opening polymerisation
rt	Room temperature
solv	Solvent
<i>tert</i> / ^{<i>t</i>}	Tertiary

TS	Transition state
----	------------------

Substituents and chemical moieties

Ac	Acetyl
Adam	Adamantyl
Ade	Adenine
Ald.	Aldehyde
Ar	Aryl
Asp	Aspartame
Bn	Benzyl
Bu	Butyl
Bz	Benzoyl
Cp*	1,2,3,4,5-Pentamethylcyclopentadienyl
Cy	Cyclohexyl
Cyp	Cyclopentyl
Epox.	Epoxide
Et	Ethyl
Form.	Formate ester
Gua	Guanine
Hal	Halogen
Het	Heterocycle
His	Histidine
ⁱ Pr	Isopropyl
Ket.	Ketone
Me	Methyl
MOM	Methoxymethyl
Ms	Mesyl
Ph	Phenyl
Pr	Propyl
Py	Pyridine
Rib	Ribozyme
Ser	Serine
^t Bu	<i>tert</i> -Butyl
Tf	Triflate
Ts	Tosyl

Reagents and Solvents

9-BBN	9-Borabicyclo[3.3.1]nonane
BNO	Brucine <i>N</i> -oxide
BVMO	Baeyer–Villiger monooxygenase
CDMT	2-Chloro-4,6-dimethoxy-1,3,5-triazine
CPMO	Cyclopentanone monooxygenase
CSA	Camphorsulfonic acid
DABCO	1,4-Diazabicyclo[2.2.2]octane
DABCOO	1,4-Diazabicyclo[2.2.2]octane <i>N</i> -oxide
DAHQ	2,5-Bis(2-methylbutan-2-yl)benzene-1,4-diol
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	<i>N,N'</i> -Dicyclohexylcarbodiimide
DCE	Dichloroethane
DCM	Dichloromethane
DIPEA	<i>N,N</i> -Diisopropylethylamine
DMAP	4-(Dimethylamino)pyridine
DMAPO	4-(Dimethylamino)pyridine <i>N</i> -oxide
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic acid
DPPCl	Diphenyl phosphoryl chloride
EDCI	<i>N</i> -Ethyl- <i>N'</i> -(3-dimethylaminopropyl)carbodiimide
[emim]	1-Ethyl-3-methylimidazolium
HBTU	<i>O</i> -(Benzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate
HFIP	1,1,1,3,3,3-Hexafluoro-2-propanol
HMPA	Hexamethylphosphoramide
HOBt	1-Hydroxybenzotriazole
<i>m</i> CBA	<i>meta</i> -Chlorobenzoic acid
<i>m</i> CPBA	<i>meta</i> -Chloroperbenzoic acid
MsCl	Methanesulfonyl chloride
MNBA	2-Methyl-6-nitrobenzoic anhydride
M.S.	Molecular sieves
MTBE	Methyl <i>tert</i> -butyl ether
MTSA	Melamine trisulfonic acid

NADPH	Reduced nicotinamide adenine dinucleotide phosphate
NADP ⁺	Nicotinamide adenine dinucleotide phosphate
NBS	<i>N</i> -Bromosuccinimide
NCS	<i>N</i> -Chlorosuccinimide
NFSI	<i>N</i> -Fluorobenzenesulfonimide
NMI-O	1-Methyl-imidazole <i>N</i> -oxide
NMM	<i>N</i> -Methylmorpholine
NMO	<i>N</i> -Methylmorpholine <i>N</i> -oxide
NMP	<i>N</i> -Methyl-2-pyrrolidone
PBA	Perbenzoic acid
PEG	Polyethylene glycol
Petrol	Petroleum ether
PMP	1,2,2,6,6-Pentamethylpiperidine
PNO	Pyridine <i>N</i> -oxide
PPNO	4-Phenylpyridine <i>N</i> -oxide
PPO	Propylene oxide
PPYO	4-Pyrrolidinopyridine <i>N</i> -oxide
PPPNO	4-(3-Phenylpropyl)pyridine <i>N</i> -oxide
PS [®]	Proton sponge, 1,8-Bis(NMe ₂)-naphthalene
PVA	Polyvinyl acetate
RNA	Ribonucleic acid
SBNPSA	Silica-bonded <i>N</i> -propyl sulfamic acid
TAPC	1,3,5-Triazo-2,4,6-triphosphorine-2,2,4,4,6,6-hexachloride
TBDPS	<i>tert</i> -Butyldiphenylsilyl
TBS	<i>tert</i> -Butyldimethylsilyl
TES	Triethylsilane
TFA	Trifluoroacetic acid
TFPAA	Trifluoroperacetic acid
THF	Tetrahydrofuran
TMNO	Trimethylamine <i>N</i> -oxide
TMSCF ₃	Trifluoromethyltrimethylsilane
TMSCN	Trimethylsilyl cyanide
TMSOF	2-(Trimethylsiloxy)furan
TPAP	Tetrapropylammonium perruthenate
TPB	Tetraphenylborate
<i>o</i> -XPCl	<i>o</i> -Xylenyl phosphoryl chloride

Table of contents

1 Introduction	1
1.1 Introduction to <i>N</i> -oxides	1
1.2 <i>N</i> -Oxides within transition metal chemistry	2
1.2.1 <i>N</i> -Oxides as ligands	2
1.2.2 <i>N</i> -Oxides as activators	5
1.2.3 Oxidation of metals	8
1.3 <i>N</i> -Oxides within organic oxidations	13
1.4 <i>N</i> -Oxides as organocatalysts	21
1.4.1 Silicon chemistry	21
1.4.1.1 Allylation reactions	22
1.4.1.2 Propargylation and allenylation reactions	35
1.4.1.3 Aldol reactions	38
1.4.1.4 Enantioselective ring opening of <i>meso</i> -epoxides	41
1.4.1.5 Cyanosilylation of carbonyl compounds and imines	47
1.4.1.6 Silylation of alcohols	56
1.4.2 Protection of alcohols	58
1.4.3 Organophosphorus chemistry	59
1.4.4 Acylation reactions	62
1.4.5 Ring opening of aziridines	67
1.4.6 Morita-Baylis-Hillman reaction	68
1.4.7 Halogenation reactions	71
1.4.8 Asymmetric tandem Michael reactions	76
1.4.9 <i>N</i> -Oxides as additives within gold catalysed reactions	78
1.4.10 <i>N</i> -Oxides as additives within enamine catalysis	80
1.5 Conclusion to review of <i>N</i> -oxides	82
2 <i>N</i>-Oxides as hydrogen bond catalysts for the Baeyer-Villiger oxidation	83
2.1 Introduction	83

2.1.1 Introduction to the Baeyer-Villiger oxidation	83
2.1.2 Overview of the mechanism	85
2.1.3 Catalytic strategies and modes of activation	91
2.1.4 Brønsted acid catalysed Baeyer-Villiger oxidations.....	93
2.1.5 Importance of proton transfer processes within the oxidation mechanism.....	95
2.1.6 Baeyer-Villiger oxidation of α,β -unsaturated ketones.....	96
2.2 Project Aims	110
2.3 Results and Discussion	114
2.3.1 Proof of principle.....	114
2.3.2 By-product isolation and characterisation	116
2.3.3 Development of conditions for the <i>N</i> -oxide promoted Baeyer-Villiger oxidation ...	125
2.3.4 Mechanistic studies.....	138
2.3.5 Synthesis of starting materials	159
2.3.6 Substrate scope	164
2.3.6.1 Baeyer-Villiger oxidation of α,β -unsaturated methyl ketones.....	165
2.3.6.2 Oxidation of 3-benzylidene-2,4-pentanedione	175
2.3.6.3 Baeyer-Villiger oxidation of chalcone derivatives	178
2.3.6.4 Baeyer-Villiger oxidation of α,β -unsaturated alkyl ketones.....	183
2.3.6.5 Baeyer-Villiger oxidation of saturated ketones	188
2.3.7 Comparison of literature methods	191
2.3.8 Base and buffer promoted Baeyer-Villiger oxidations	193
2.3.9 Reactions of 3-(4-methoxyphenyl)but-3-en-2-one	202
2.3.10 Optimisation for by-product formation	213
2.3.10.1 Formation of epoxy ester	213
2.3.10.2 Synthesis of α -acetoxy aldehyde	214
2.3.10.3 Synthesis of formate ester.....	217
2.4 Conclusion.....	222
2.5 Future work	224

3 Investigating (formyloxy)(phenyl)methyl acetate as a novel formylating reagent	227
3.1 Introduction.....	227
3.1.1 Applications of formamides.....	227
3.1.2 <i>N</i> -Formylating reagents.....	229
3.1.3 Formate esters and formamides as <i>N</i> -formylating reagents	232
3.2 Project aims.....	243
3.3 Results and Discussion	244
3.3.1 Development of <i>N</i> -formylation methodology using (formyloxy)(phenyl)methyl acetate	244
3.3.2 Scope of primary and secondary amines.....	250
3.3.3 <i>N</i> -Formylation of a carboxyl protected amino acid	254
3.3.4 <i>N</i> -Formylation of an unprotected amino acid	255
3.3.5 Developing a one pot synthesis of isocyanides from amines	256
3.3.6 <i>O</i> -Formylation of primary alcohols	257
3.4 Conclusion	260
4 <i>N</i>-Oxides as organocatalysts for electrophilic aromatic brominations	261
4.1 Introduction.....	261
4.1.1 Electrophilic aromatic brominations	261
4.1.2 <i>N</i> -Oxides as catalysts within bromination reactions	265
4.2 Project Aims.....	268
4.3 Results and Discussion	269
4.3.1 Development of <i>N</i> -oxide catalysed methodology	269
4.3.2 Development of iodide catalysed methodology	279
4.3.3 Optimisation of work-up procedure	284
4.3.4 Bromination of toluene	285
4.4 Conclusion	287
4.5 Future work.....	288
5 Experimental	290

5.1 General Experimental Information	290
5.2 Experimental procedures and compound characterisation data for Chapter 2	293
5.2.1 General procedures for starting material synthesis.....	293
5.2.2 Standard work-up procedure	294
5.2.3 Iodometric titration to determine the purity of <i>m</i> CPBA.....	294
5.2.4 General procedures for the optimisation of Baeyer-Villiger methodology	295
5.2.5 Procedures for mechanistic studies.....	296
5.2.6 Procedures for examining the substrate generality	298
5.2.7 General procedures for vinyl ester synthesis	299
5.2.8 General procedures for reactions of 3-(4-methoxyphenyl)but-3-en-2-one (485)	299
5.2.9 General procedures for the optimisation of by-products encountered.....	299
5.2.10 Experimental Data	300
5.3 Experimental procedures and compound characterisation data for Chapter 3	338
5.3.1 Procedures for optimisation of formylation methodology.....	338
5.3.2 General procedures for formamide synthesis	339
5.3.3 Experimental Data	340
5.4 Experimental procedures and compound characterisation data for Chapter 4	350
5.4.1 General procedures for optimisation studies	350
5.4.2 Experimental Data	352
6 Appendix: Single crystal X-ray diffraction data for (1<i>S</i>,3<i>R</i>,6<i>R</i>,8<i>S</i>)-3,6-bis(4-methoxyphenyl)-1,8-dimethyl-2,7,9-trioxatricyclo[4.3.0.0^{3,8}]nonane (487)	354
7 References	361

1 Introduction

1.1 Introduction to *N*-oxides

Amine *N*-oxides are chemical compounds of the general formula $R_3N^+-O^-$ that are characterised by a nitrogen-oxygen dative bond.¹ The nitrogen atom within this functional group can either be sp^2 or sp^3 hybridised, with the former being common in heteroaromatic *N*-oxides for which the $2p\pi$ electrons on the oxygen are in conjugation with the π -system of the ring (Figure 1).^{1,2} For sp^3 hybridised systems, such as trimethylamine *N*-oxide, the nitrogen atom exists in a tetrahedral environment, as determined by X-ray crystallographic studies.¹ Due to the compound's inability to invert at the nitrogen centre, *N*-oxide species bearing three inequivalent substituents are chiral unlike the parent amines (Figure 2).^{1,2}

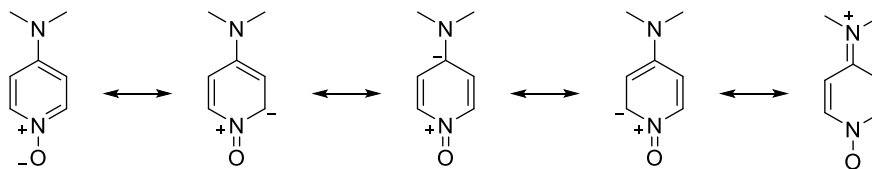


Figure 1. Resonance forms of 4-dimethylaminopyridine *N*-oxide.³

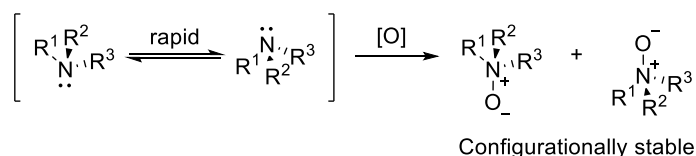
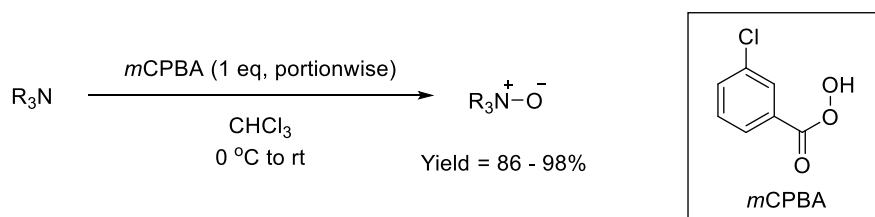


Figure 2. Chirality of amine *N*-oxides containing three different alkyl substituents.^{1,2}

N-Oxides possess exceptionally large dipoles and as a result of their polar nature exhibit the following properties: high solubility in water and other polar solvents, ability to act as hydrogen bond acceptors, high hygroscopicity and Lewis basicity.^{1,2} Exploitation of this latter property features prominently within the chemistry of *N*-oxides and will form the primary focus of this review.¹ For instance, the electron pair donor ability of *N*-oxides enables them to form complexes with Lewis acids as well as function as ligands in metal complexes and organocatalysts.² Additionally, the application of *N*-oxides as hydrogen bond catalysts will be discussed.

N-Oxides are typically prepared from the oxidation of the corresponding amine using hydrogen peroxide or more commonly *meta*-chloroperbenzoic acid (*m*CPBA) as the oxidant.^{1,2,4,5} A typical procedure for the synthesis of *N*-oxides involves the portionwise addition of an equimolar quantity of *m*CPBA to a solution of the parent amine in chloroform at low temperatures, as shown in Scheme 1.⁶



Scheme 1. Synthesis of *N*-oxides from the oxidation of tertiary amines with *m*CPBA.⁶

The applications of *N*-oxides are numerous and include their use as protecting groups, oxidants as well as intermediates in synthesis.^{6,7} *N*-Oxides are also important in their own right, as they exhibit interesting biological activity and have found application within the pharmaceutical and agrochemical industries.⁷ For instance, Minoxidil (**1**) has been approved for the treatment of hypertension and alopecia,^{8,9} whilst substituted pyridine *N*-oxides such as **2** have been utilised as herbicides (Figure 3).¹⁰ Additionally, *N*-methylmorpholine *N*-oxide (NMO, **3**) is employed as an ionic solvent within the industrial scale Lyocell process, which produces fibres from cellulose for the production of fabrics (Figure 3).^{11,12}

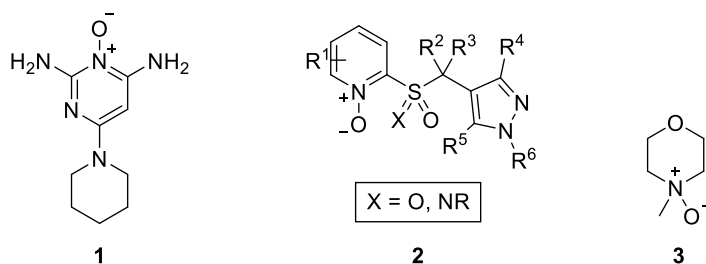


Figure 3. Industrially important *N*-oxides.⁸⁻¹²

1.2 *N*-Oxides within transition metal chemistry

1.2.1 *N*-Oxides as ligands

N-Oxides have been documented as neutral ligands for metal catalysts since the 1970s, with heteroaromatic, sp^2 hybridised *N*-oxides being most commonly employed.^{1,2,7} Specifically, the *N*-oxide coordinates to the metal centre through its oxygen atom and can act as a monodentate, polydentate or bridging ligand depending on the nature of the system (Figure 4).⁷ Unlike the parent amines, *N*-oxides do not generally have the associated problem of poisoning the metal catalyst as they are more weakly coordinating.⁷ However, as a result of the intrinsic weakness of the $\text{N}\rightarrow\text{O}$ bond ($\sim 65 \text{ kcal mol}^{-1}$), *N*-oxides are often utilised in conjunction with higher oxidation state metal complexes in order to prevent oxygen transfer processes occurring (see section 1.2.3).^{1,7} Until more recently, the application of *N*-oxides as ligands within the general arena of transition metal catalysis and more specifically their use as chiral ligands within asymmetric

catalysis remained largely unexplored.^{1,2} This topic is the focus of a comprehensive review published by Feng and co-workers.²

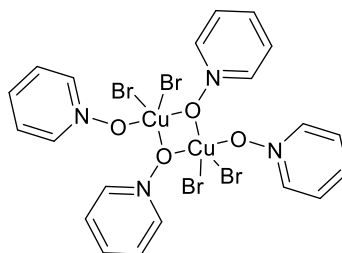
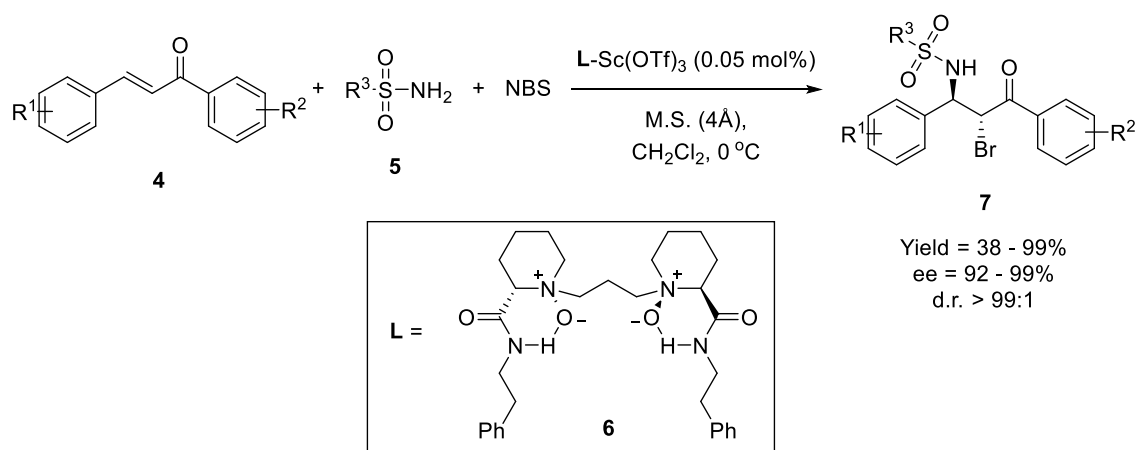
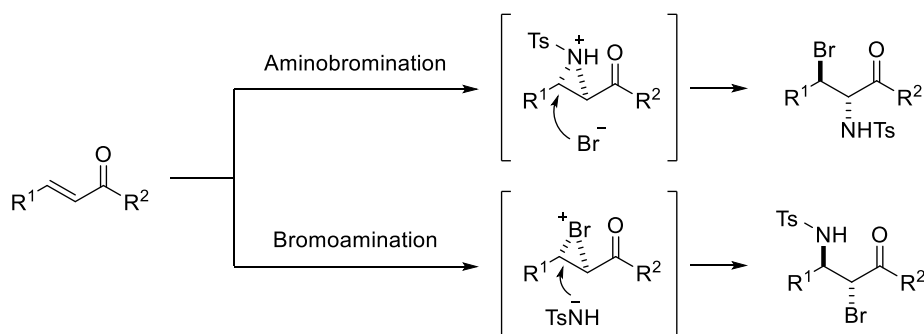
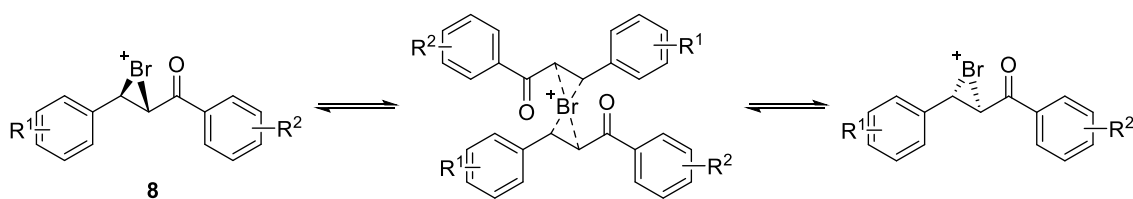


Figure 4. Copper complex containing pyridine *N*-oxides as neutral monodentate and bridging ligands.⁷

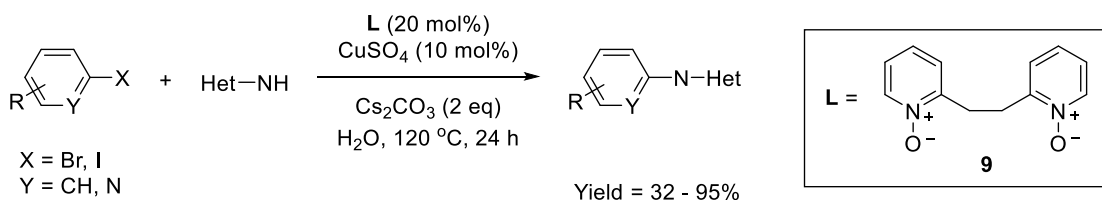
A representative example of a catalytically useful metal *N*-oxide complex is the *N,N'*-dioxide **6** / scandium(III) complex shown in Scheme 2, which was reported by Feng *et al.* in 2010 for the asymmetric bromoamination of chalcones.^{2,13} Typically, this difunctionalisation suffers from low regioselectivities, due to a competing aminobromination reaction (Scheme 3), and low enantioselectivities, which has been attributed to racemisation of the intermediate bromonium ion **8** (Scheme 4).^{2,13} This methodology represents the first catalytic system for the synthesis of α -bromo- β -amino ketone derivatives **7** in high enantioselectivities and diastereoselectivities.^{2,13} High yields were generally attained and the substrate scope was excellent with respect to both the chalcone substrate **4** and the sulfonamide nucleophile **5**.^{2,13}



Scheme 2. Asymmetric bromoamination of chalcones catalysed by an *N,N'*-dioxide/Sc(III) complex.¹³

Scheme 3. Competing aminobromination and bromoamination of chalcones.¹³Scheme 4. Racemisation mechanism of intermediate bromonium ion **8**.¹³

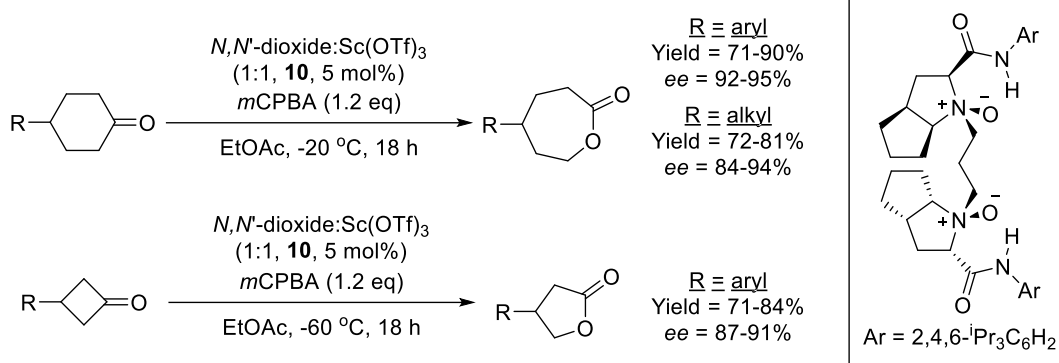
N-Oxides are also employed as ligands to take advantage of their unique physical properties. For instance, in 2009 Zhou and co-workers reported that the copper catalysed *N*-arylation of imidazole derivatives with aryl halides could successfully be conducted in water when employing bidentate bis-*N*-oxide ligand **9** (Scheme 5).¹⁴

Scheme 5. Copper catalysed *N*-arylation of imidazoles.¹⁴

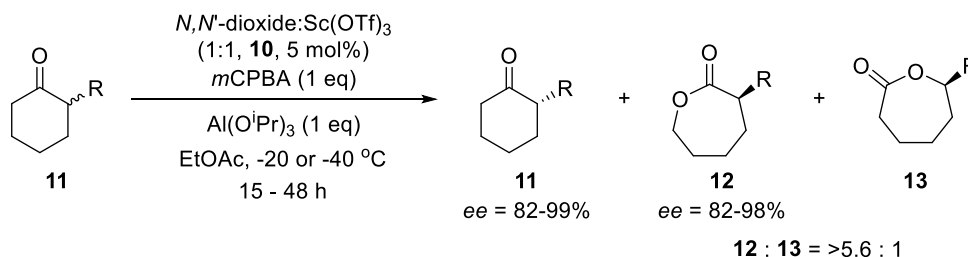
Of particular relevance to the work reported herein, Feng *et al.* have demonstrated that chiral *N,N'*-dioxide-Sc^{III} complex **10** promotes the enantioselective Baeyer-Villiger oxidation of cyclic ketones; allowing for the desymmetrisation of prochiral species and kinetic resolution of racemic derivatives (Scheme 6).¹⁵ A range of enantioenriched lactones were successfully prepared in high yields (71-90%) and enantioselectivities (84-95%) from the oxidation of symmetrical cyclohexanones and cyclobutanones with *m*CPBA catalysed by **10**.¹⁵ The highest optical purities were obtained for aromatic substituted species (87-95% *ee*) and in particular for the larger cyclohexanone ring, with asymmetric induction unaffected by both the electronics and sterics of the aryl group.¹⁵ For the alkyl substituted cyclohexanone congeners the highest enantioselectivities were observed for the more bulky substituents (84-94%).¹⁵ The kinetic resolution of 2-arylcycloalkenones **11** was also described, with the *R* enantiomer preferentially undergoing

oxidation.¹⁵ Interestingly, due to the steric hindrance imparted by the *N,N'*-dioxide ligand in the transition state, migration of the less sterically encumbered CH₂ group of **11** was observed; affording the ‘abnormal’ lactone **12** as the major product (**12/13**: 5.6/1 to >19/1).¹⁵ The lactone **12** (82-98% *ee*) and remaining unreacted ketone **11** (82-99% *ee*) were both isolated with excellent optical purity and high conversions were reported (47.7-52.3%).¹⁵

a) Desymmetrisation



b) Kinetic resolution

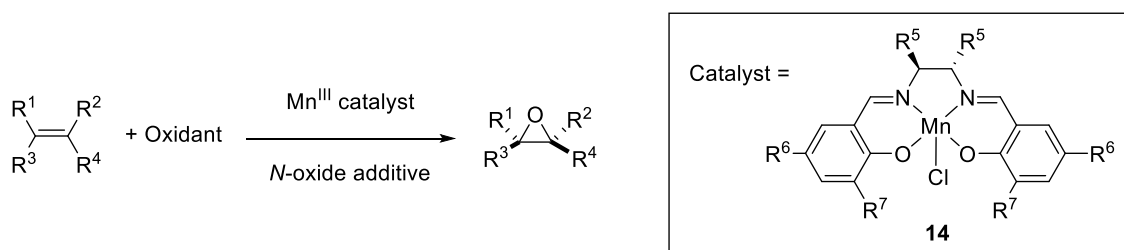


Scheme 6. Chiral *N,N'*-dioxide-Sc^{III} complex **10** promoted enantioselective Baeyer-Villiger oxidation of cyclic ketones.¹⁵

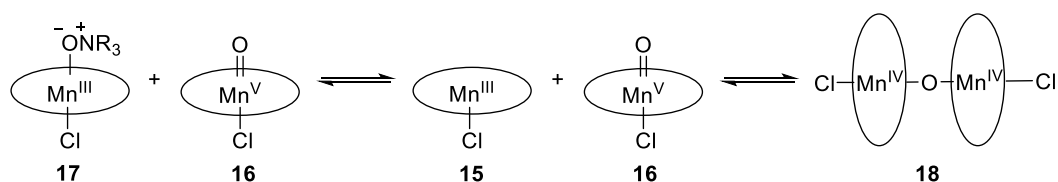
1.2.2 *N*-Oxides as activators

N-Oxides may also activate transition metal-based species towards further reaction or prevent deactivation of the metal catalyst. A wealth of literature exists concerning the use of *N*-oxides as axial ligands for Mn(III) salen-based catalysts (**14**), which are used to promote the enantioselective epoxidation of olefins (Scheme 7).¹⁶⁻³¹ *N*-Oxides have been observed to enhance the reaction rate, product yield and/or enantioselectivity of these transformations.¹⁶⁻³¹ In this context, 4-phenylpyridine *N*-oxide (PPNO),¹⁶⁻¹⁹ pyridine *N*-oxide (PNO),¹⁹⁻²⁵ lutidine *N*-oxide,²³ *N*-methylmorpholine *N*-oxide (NMO)^{26,27} and 4-(3-phenylpropyl)pyridine *N*-oxide (PPPNO)²⁸ have been applied as donor ligands in conjunction with a range of oxidising agents.²⁴ Mechanistic studies, performed by Jacobsen *et al.* and others, suggest that the *N*-oxide is not acting as an oxidant but instead binds to Mn(III) species **15** to form **17**, preventing formation of catalytically inactive dimer **18** and therefore enhancing the rate of reaction (Scheme 8).^{18,19,24,25} Therefore, the primary role of the *N*-oxide is to ensure that the concentration of active Mn(V) oxo species **16** remains high.^{1,18,19,24,25} It has been proposed by some that the improved enantioselectivities

observed when the reaction is conducted in the presence of *N*-oxides can be attributed to a conformational change within the catalyst upon binding of the ligand.²³ Alternatively, Jacobsen has suggested that for NaOCl promoted oxidations, the *N*-oxide may prevent a competing, nonselective epoxidation pathway; resulting in enhanced enantioselectivities.¹⁸

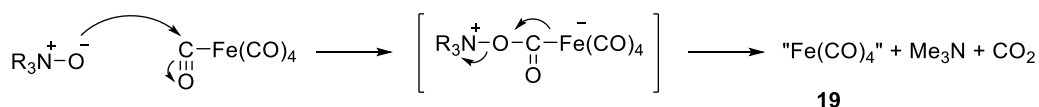


Scheme 7. Manganese catalysed enantioselective epoxidation of olefins.²⁶



Scheme 8. Equilibria of manganese species in solution.¹⁹

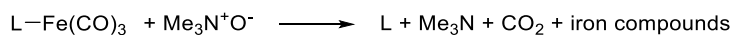
A seminal study into oxygen transfer reactions between amine *N*-oxides and metal carbonyl compounds was conducted by Hieber and co-workers in 1959.³²⁻³⁴ Specifically, the authors investigated the deoxygenation of amine *N*-oxides by $\text{Fe}(\text{CO})_5$ (Scheme 9).³²⁻³⁴ Shortly after this publication, Alper and Edward proposed that the reaction proceeds *via* initial nucleophilic attack of the *N*-oxide at a metal bound carbonyl group to generate CO_2 and a new metal carbonyl complex **19** (Scheme 9).^{5,32-34}



Scheme 9. Deoxygenation of amine *N*-oxides by $\text{Fe}(\text{CO})_5$.^{32,34}

In related work, Shvo *et al.* demonstrated that *N*-oxides, particularly trimethylamine *N*-oxide (TMNO), can be used to liberate organic molecules from iron carbonyl complexes (Scheme 10) or alternatively can be employed to facilitate complexation of ligands to iron carbonyl complexes (Scheme 11).^{5,35,36} This methodology has since been extended to other group 8 metals (Fe, Ru and Os) as well as the group 6 triad (Cr, Mo and W).^{5,32,37,38} The generally accepted mechanism involves initial decarboxylation of the metal carbonyl complex, as alluded to previously, with subsequent rapid coordination of a nucleophile to the coordinatively unsaturated carbonyl

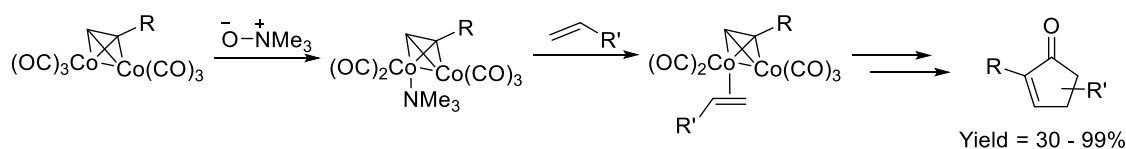
complex **19**.^{5,32,37,38} This type of metal carbonyl complex activation protocol has been successfully applied to a range of synthetically useful transformations, including: the Pauson-Khand reaction (Scheme 12),³⁹ the hydroesterification of olefins with alkyl formates (Scheme 13),⁴⁰ alcohol oxidation processes (Scheme 14)^{41,42} and the decarbonylation of alkyl formates to alcohols (Scheme 15).⁴³



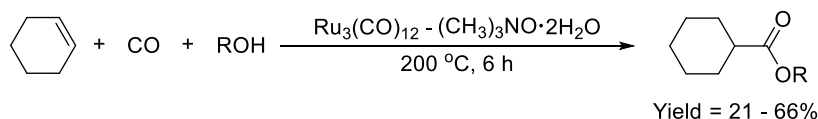
Scheme 10. Liberation of an organic ligand from iron carbonyl complexes using TMNO.³⁵



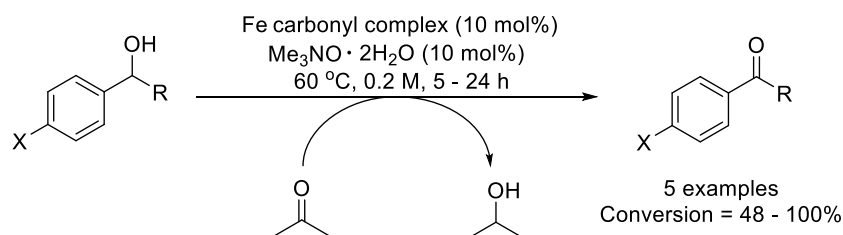
Scheme 11. TMNO promoted complexation of an organic ligand to an iron carbonyl complex.³⁵



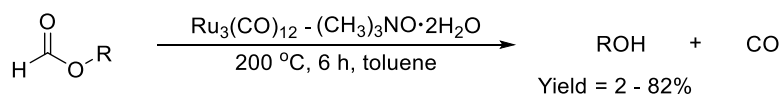
Scheme 12. TMNO initiated Pauson-Khand reaction.³⁹



Scheme 13. TMNO initiated hydroesterification of olefins with alkyl formates.⁴⁰



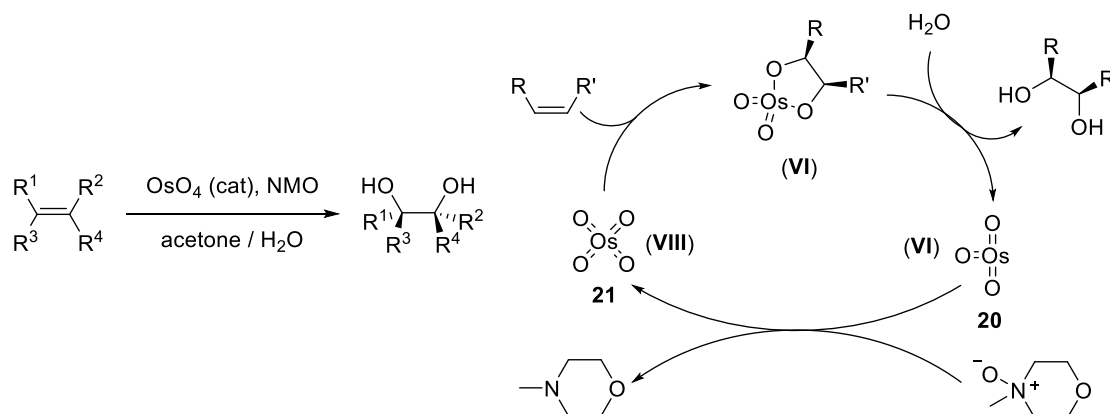
Scheme 14. TMNO initiated oxidation of alcohols to their corresponding aldehydes and ketones.⁴¹



Scheme 15. TMNO initiated decarbonylation of alkyl formates to alcohols.⁴³

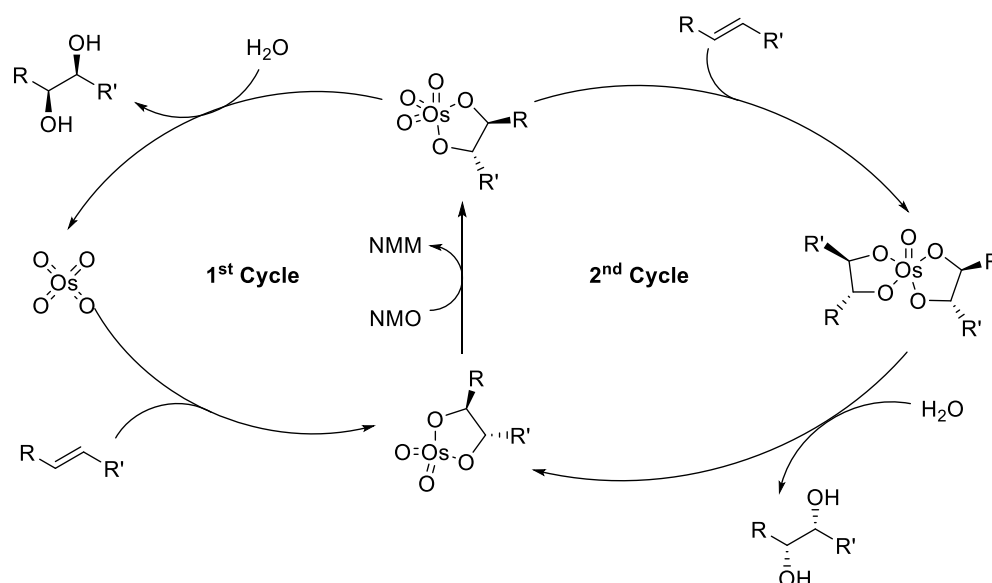
1.2.3 Oxidation of metals

Owing to the intrinsic weakness of the N→O bond, N-oxides have also found application as oxidants for metal complexes. For instance, the osmium tetroxide promoted dihydroxylation of olefins represents a important method for synthesising vicinal diols (Scheme 16).^{44,45} Within this system, NMO has proven to be a particularly suitable co-oxidant, allowing for the highly toxic and expensive osmium reagent to be employed in catalytic quantities.^{1,44,45} As shown in Scheme 16, NMO reoxidises Os(VI) (**20**) to the catalytically active Os(VIII) species **21**.⁴⁶



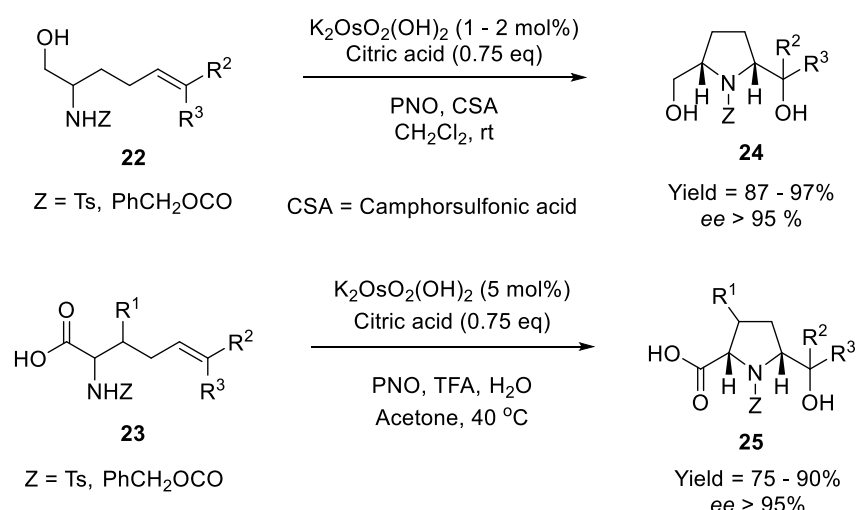
Scheme 16. NMO as an oxidant for the Upjohn dihydroxylation reaction of olefins.⁴⁶

This methodology was initially developed at The Upjohn Company by VanRheenen and co-workers for the racemic dihydroxylation reaction and was subsequently applied to the Sharpless asymmetric variant.^{44,45,47,48} Sharpless *et al.* concluded that the oxidation protocol could be extended to a wide range of substrates and that the rate of reaction could be enhanced by the addition of cinchona alkaloid derivatives.^{1,44,47} However, the enantioselectivities were compromised (20 – 80% *ee*), particularly for aliphatic and terminal olefins, which was attributed to a competing catalytic cycle where the chiral ligand was not involved and therefore enantiodiscrimination was not achieved (Scheme 17).^{44,47,49-51} Progress has been made towards overcoming the poor asymmetric induction, with several different approaches being reported, including: the development of alternative chiral ligands,^{44,49,50,52-56} adopting a slow addition protocol,⁵⁷ utilising OsO₄²⁻ immobilised on resin,⁵⁸ altering the solvent system to reduce the solubility of the alkene^{49,52,55} and employing ionic liquids.^{59,60}



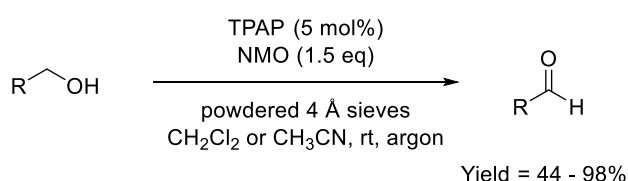
Scheme 17. Competing catalytic pathways for the Sharpless dihydroxylation reaction.^{44,49,50}

More recently, pyridine *N*-oxide (PNO) has been employed by Donohoe and co-workers as a mild reoxidant for the osmium tetroxide catalysed oxidative cyclisation of *N*-tosyl amino alcohols **22** and acids **23**, which contain a remote alkene moiety, to their corresponding pyrrolidine derivatives **24** and **25** (Scheme 18).⁶¹ Within this system, the active catalyst for the cyclisation reaction has been identified as Os(VI), whilst Os(VIII) conversely results in competing, undesired dihydroxylation of the alkene functionality.⁶¹ Of particular significance is the finding that PNO, unlike TMNO and NMO, can oxidise osmium to the catalytically active Os(VI) oxidation state, without undesired over oxidation to Os(VIII).^{61,62} This finding removed the need for the presence of excess quantities of a sacrificial alkene in these protocols.^{61,62}



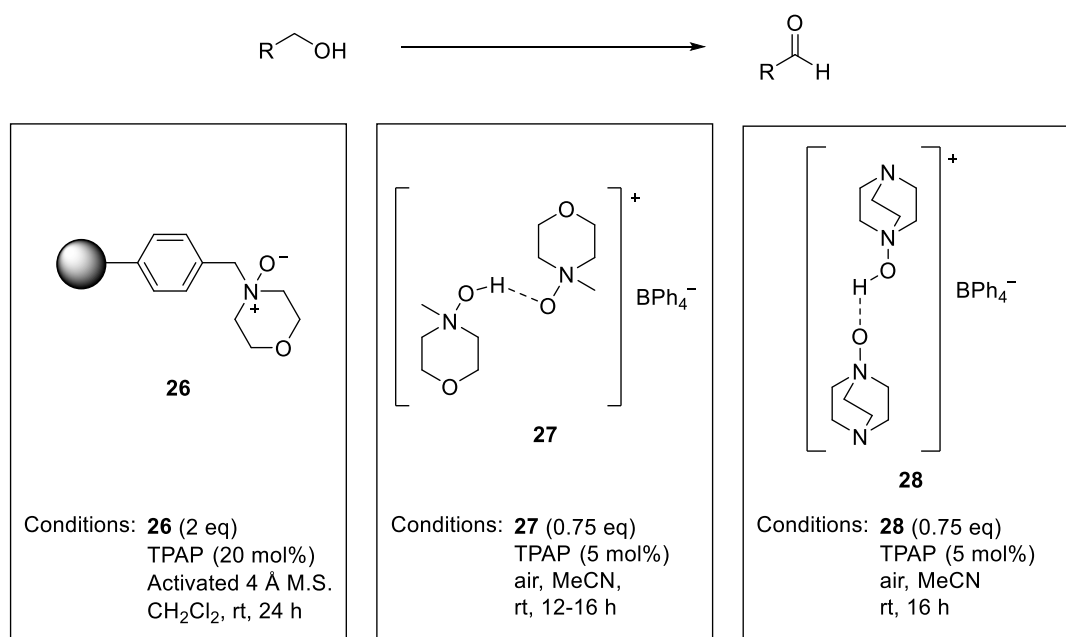
Scheme 18. Osmium catalysed oxidative cyclisation of *N*-tosyl amino alcohols and acids.⁶¹

NMO is also frequently employed as a stoichiometric oxidant for the tetrapropylammonium perruthenate (TPAP) catalysed oxidation of alcohols to their corresponding aldehydes and ketones under anhydrous conditions (Scheme 19).^{1,63} Such rigorously dry conditions were necessary to prevent over-oxidation of the desired aldehyde to the corresponding carboxylic acid.^{63,64} Accordingly, due to the high hygroscopicity of NMO and the production of water as a by-product, oxidations were performed in the presence of molecular sieves.^{63,64} Typically, this transformation is high yielding even for allylic systems (73-82%) and less hindered alcohols exhibit the highest rates of reaction, with examples of primary alcohols being selectively oxidised in the presence of secondary alcohols.⁶³ This methodology has also been successfully extended to the oxidation of diols and lactols to lactones, as well as for heteroatom oxidation reactions.⁶³



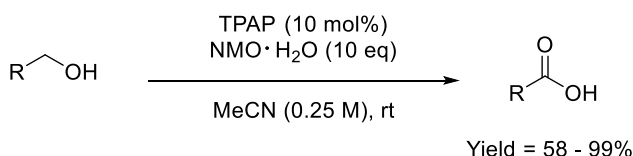
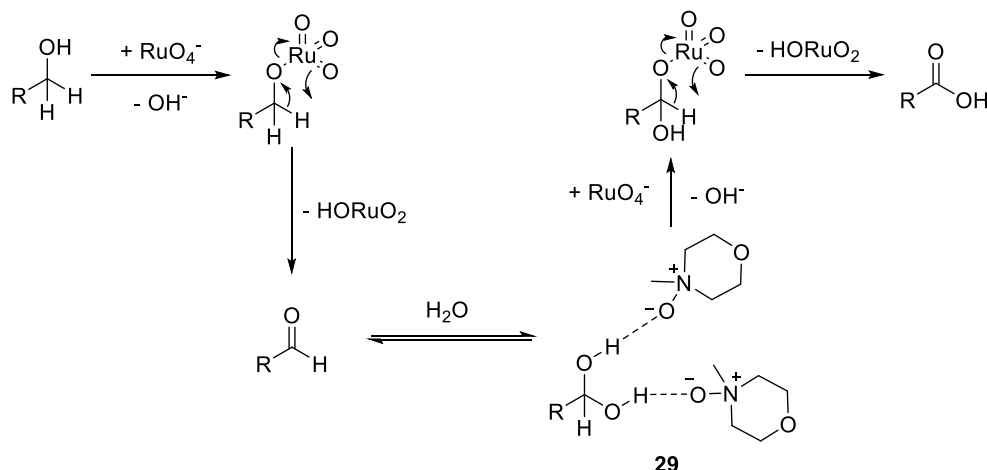
Scheme 19. TPAP catalysed oxidation of alcohols to afford aldehydes/ketones.⁶³

Several variations of the catalytic system have been reported in recent years (Scheme 20).⁶⁴⁻⁶⁶ For instance, Kerr *et al.* determined that recyclable, polymer bound *N*-methylmorpholine *N*-oxide **26** could be successfully employed as the co-oxidant within the Ley-Griffith oxidation of alcohols, which reduces the associated waste.⁶⁶ In 2015, Williams and co-workers reported that application of non-hygroscopic tetraphenylborate (TPB) salt **27** allowed for the controlled oxidation of alcohols to be conducted without air exclusion and the need for molecular sieves.⁶⁵ Subsequently, the authors explored a range of salts for this purpose, which similarly contained no water of crystallisation, and identified **28** (DABCOO•TPB) as a promising alternative.^{64,65} The high reactivity of **28** has been attributed to the reduced steric hindrance about the oxygen of the *N*-oxide moiety within this caged structure, which may promote more facile regeneration of the active catalyst.⁶⁴ In accordance with the traditional Ley-Griffith oxidation, activated primary alcohols such as allylic and benzylic species were found to exhibit superior reactivity for all three catalytic systems developed.⁶⁴⁻⁶⁶ Additionally, chemoselective oxidation of such activated primary alcohols was achieved in the presence of other primary hydroxyl species.⁶⁴⁻⁶⁶

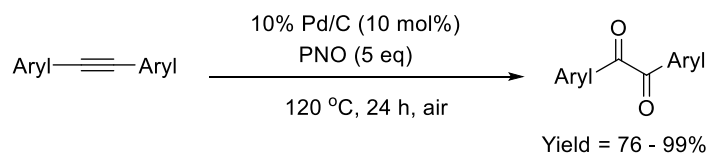


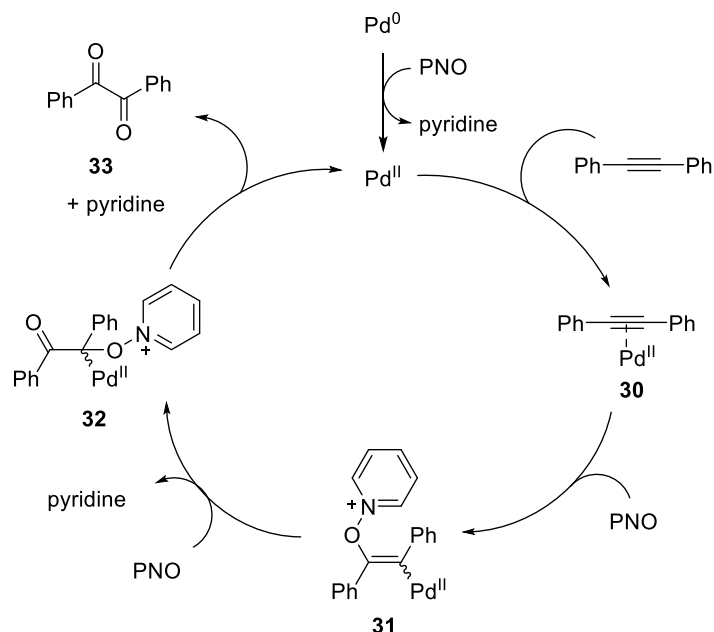
Scheme 20. Variations to the *N*-oxide co-oxidant within the TPAP mediated oxidation of alcohols.⁶⁴⁻⁶⁶

Stark *et al.* have provided the first comprehensive study into the use of this system for the one pot oxidation of primary alcohols into carboxylic acids in the presence of water (Scheme 21).^{67,68} The authors proposed that the vastly improved efficiency of this reaction in the presence of NMO was attributable to favourable hydrogen bonding interactions acting to stabilise the aldehyde hydrate intermediate (**29**, Scheme 22).^{67,68} More specifically, NMO and the hydrate were found to associate as 1:1 hydrogen bonded pairs in solution, as determined from Job Plot experiments.⁶⁸ Analysis by single crystal X-ray diffraction of the co-crystals obtained for chloral hydrate with various *N*-oxides also displayed a 1:1 hydrogen bonded complex in the solid state.⁶⁸ The crystal structure showed each Lewis basic *N*-oxide molecule interacting with 2 hydrate molecules and vice versa *via* moderate strength hydrogen bonds in either a ring or linear arrangement depending on the exact identity of the *N*-oxide.⁶⁸ However, it is unclear whether such bonding arrangements are maintained in solution.⁶⁸ Nevertheless, such stabilising interactions perturb the equilibrium to some extent towards the normally unstable aldehyde hydrate **29**, which is unfavourable on both entropic and enthalpic grounds; increasing its concentration in solution and therefore enhancing the reaction rate.^{67,68} The authors also speculate that the *N*-oxide may act as a catalyst for the generation of the aldehyde hydrate but do not elaborate on this any further.^{67,68} Interestingly, in this system the *N*-oxide also functions as a secondary oxidant to regenerate the Ru(VII) species and provides a source of water *via* an NMO-water complex that does not deactivate the catalyst.^{67,68}

Scheme 21. TPAP catalysed oxidation of alcohols to afford carboxylic acids.⁶⁷Scheme 22. Mechanism of TPAP catalysed oxidation of alcohols to afford carboxylic acids.^{67,68}

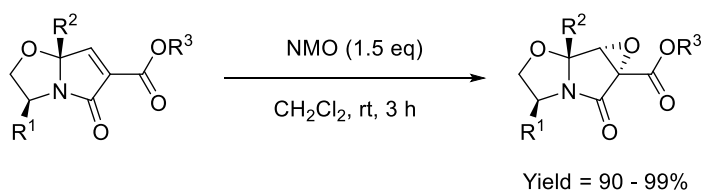
In 2011, Sajiki *et al.* published their findings on the use of PNO as an oxidant for the Pd/C catalysed preparation of 1,2-diaryl-1,2-diketones from their corresponding diarylalkynes, using the optimised conditions shown in Scheme 23.⁶⁹ Mechanistically, the authors propose that PNO initially oxidises the Pd⁰ precatalyst *in situ* to form the catalytically active Pd(II) species (Scheme 24).⁶⁹ Coordination of the alkyne to this Pd(II) complex generates **30**, which activates the alkyne towards nucleophilic attack by a further molecule of PNO, forming intermediate **31**.⁶⁹ Oxidation of **31** by a third equivalent of PNO generates intermediate **32**, which upon elimination of pyridine affords the desired diketone (**33**) and regenerates the active Pd(II) species.^{69,70} As the *N*-oxide also functions as the solvent, its role can be considered three-fold, with this methodology highlighting the ability of *N*-oxides to act as oxidants not only to metals but also organic substrates.⁶⁹

Scheme 23. Oxidation of diarylalkynes to afford 1,2-diaryl-1,2-diketones.⁶⁹

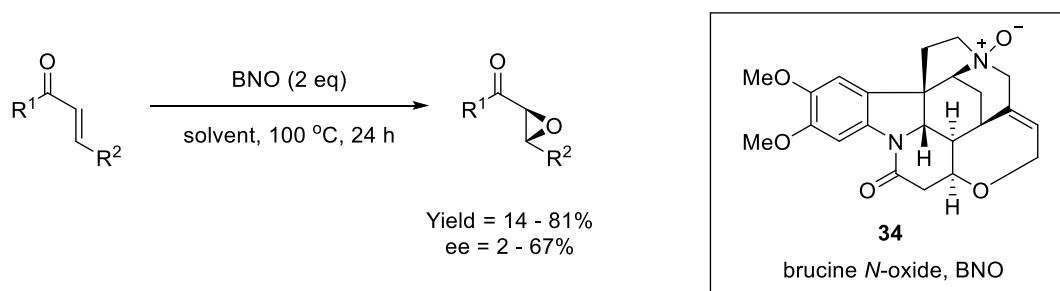
Scheme 24. Mechanism of Pd(II) diarylalkyne oxidation reaction.⁶⁹

1.3 N-Oxides within organic oxidations

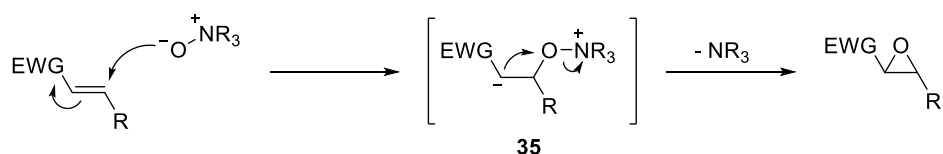
Tertiary amine *N*-oxides have also been employed as oxidants for a range of organic compounds in the absence of metals.⁵ One relatively recent example of this is the asymmetric oxidation of unsaturated substrates; such as lactams⁷¹ and α,β -unsaturated ketones.⁷² For example, Meyers *et al.* demonstrated that NMO can successfully be used to promote the stereospecific epoxidation of unsaturated bicyclic lactams, with excellent yields achieved (Scheme 25).⁷¹ However, the substrate scope of this reaction was found to be restricted to lactams that contain a double bond with two geminal carbonyl groups.⁷¹

Scheme 25. Stereospecific epoxidation reaction of unsaturated bicyclic lactams using NMO.⁷¹

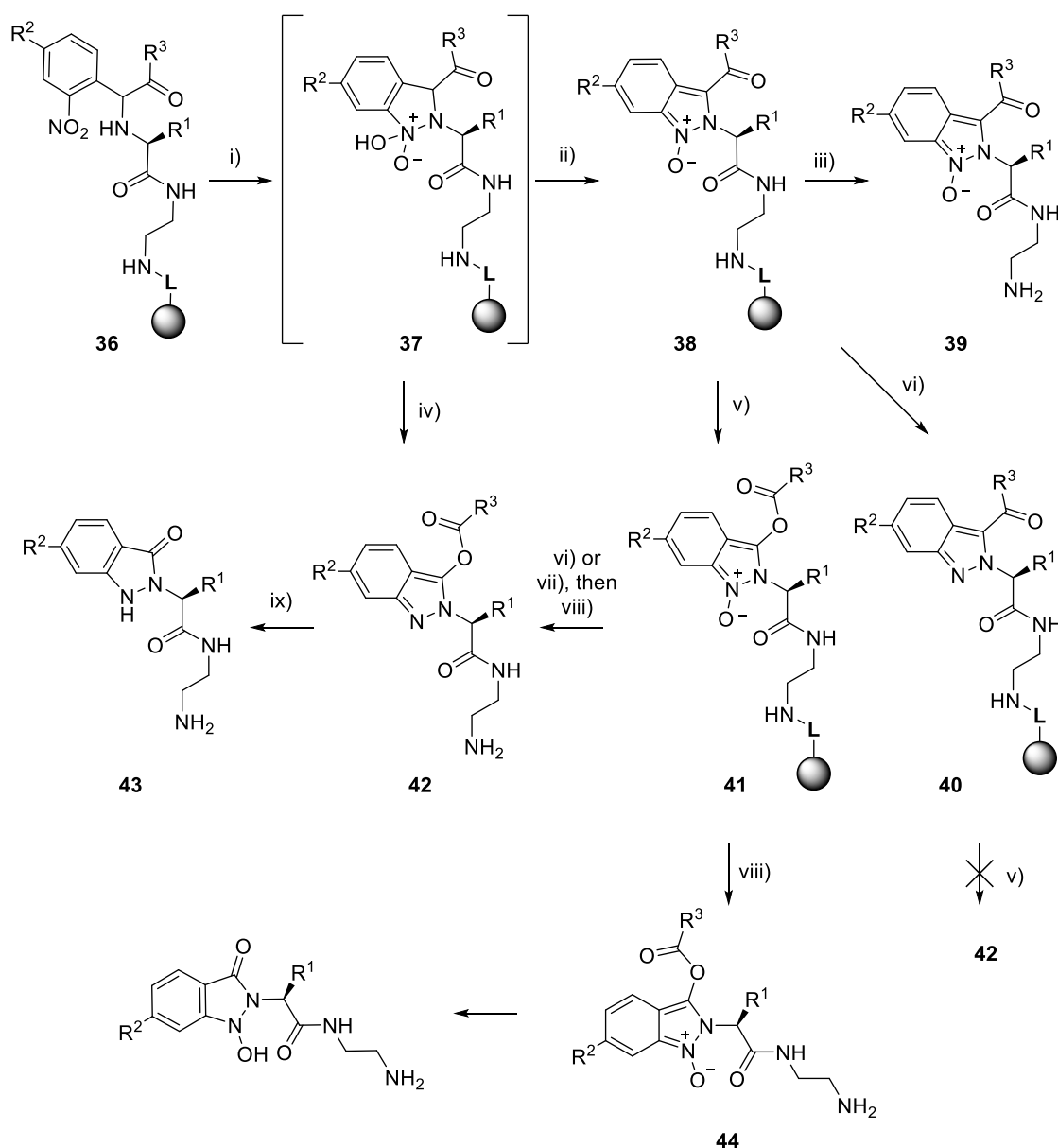
In 2008, Oh *et al.* reported that chiral brucine *N*-oxide (BNO) **34** participates in the stereoselective oxidation of chalcone derivatives to afford the corresponding epoxides with poor to good enantioselectivities (Scheme 26).⁷² During optimisation studies, it was observed that the nature of the solvent and the reaction concentration significantly influenced the yield and enantioselectivity obtained, with reoptimisation of these parameters often being required for each substrate.⁷²

Scheme 26. Stereoselective epoxidation of chalcone derivatives using BNO.⁷²

Mechanistically, it has been proposed that the epoxidation is initiated by 1,4-conjugate addition of the *N*-oxide to the electron deficient alkene (Scheme 27), which for the lactam substrates shown in Scheme 25 occurs at the least hindered face.^{71,72} Within intermediate **35**, the oxygen atom is then attacked by the enolate fragment to generate the epoxide ring and an equivalent of the tertiary amine, as shown in Scheme 27.^{71,72}

Scheme 27. Mechanism of epoxidation by *N*-oxides.^{71,72}

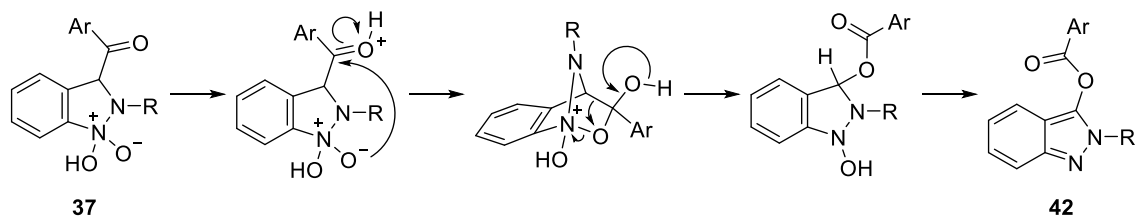
In 2016, Krchňák and Schütznerová reported an unprecedented intramolecular oxidation of a ketone to the corresponding ester, reminiscent of the Baeyer-Villiger oxidation, by participation of a neighbouring *N*-oxide moiety without the use of an external oxidant (Scheme 28).⁷³ Within this study, indazole oxide **38** was prepared *via* a multistep synthesis concluding with spontaneous dehydration of intermediate **37**.⁷³ Indazole oxide **38** was found to undergo facile Baeyer-Villiger oxidation under traditional conditions using *m*CPBA as the oxidant, with only a single regioisomer of the ester **41** formed.⁷³ Subsequent deoxygenation of the *N*-oxide with mesyl chloride or alternatively a sodium dithionite reduction afforded a mixture of indazol-3-yl ester **42** and hydrolysis product **43**.⁷³ Curiously, indazol-3-yl ester **42** could not be prepared by performing these steps in reverse, as the corresponding parent indazole **40** is inert to oxidation by *m*CPBA under identical conditions.⁷³ Treatment of both the solid supported ketone and ester derivatives **38** and **41** with TFA in DCM at room temperature for 1 hour resulted exclusively in cleavage of these species from the resin to afford **39** and **44** respectively.⁷³ Surprisingly, analogous treatment of intermediate **37** with TFA not only resulted in cleavage of the resin but also direct access to the oxidised species, ester **42**.⁷³ A small range of these pharmacologically interesting species and their hydrolysed derivatives **43** were then synthesized in low to moderate yield using the developed method (**42**: 16-33%, **43**: 22-52%).⁷³



i) DBU (0.2 M), DMF, rt, 30 min; ii) DMF, rt, 24 h; iii) TFA (reagent grade), CH₂Cl₂, rt, 1 h; iv) TFA (redistilled), CH₂Cl₂ (anhydrous), rt, 1 h; v) *m*CPBA (0.5 M), CH₂Cl₂, rt, 30 min - 24 h; vi) TEA (0.7 M), CH₂Cl₂, 0 °C; then MsCl (0.5 M), CH₂Cl₂, rt, 24 h; vii) Na₂S₂O₄, K₂CO₃, (tBu₄N)HSO₄, H₂O/CH₂Cl₂ (1 : 1), rt, 2 h; viii) TFA, CH₂Cl₂ (1 : 1), rt, 1 h; ix) H₂O, MeOH, rt, 24 h.

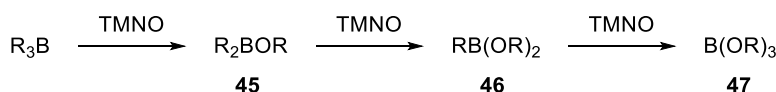
Scheme 28. Intramolecular oxidation of ketone **36** into ester **42** involving participation of a neighbouring *N*-oxide moiety.⁷³

The authors have tentatively proposed that the dry, acidic conditions promote intramolecular cyclisation and rearrangement, which is comparable to the mechanism of the Baeyer-Villiger oxidation, with subsequent dehydration giving the observed product **42** (Scheme 29).⁷³ Thus, the *N*-oxide moiety within intermediate **37** appears to be functioning as an internal oxidising agent.⁷³



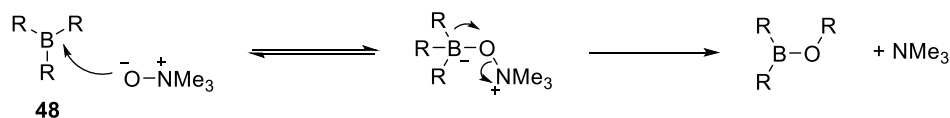
Scheme 29. Proposed mechanism for the formation of ester **42** from *N*-oxide intermediate **37**.⁷³

Koster and co-workers were the first to demonstrate that organoboranes could undergo consecutive oxidation by anhydrous tertiary amine *N*-oxides to afford borinate **45**, boronate **46** or borate esters **47**, as governed by the stoichiometry of the oxidant and reaction conditions employed (Scheme 30).^{5,74-77} If required, the corresponding alcohols can then be obtained *via* transesterification of the alkoxyborane with an alcoholic solvent.^{74,76} This methodology has also been extended to the synthesis of aldehydes, ketones and carboxylic acids from 1,1-diboryl-alkanes, 2,2-diboryl-alkanes and 1,1,1-triboryl-alkanes respectively, which is not possible using other oxidants due to competing protonolysis of their boron-carbon bonds.⁷⁷ Boron-nitrogen as well as boron-hydrogen linkages have also been successfully oxidised using TMNO.⁷⁷



Scheme 30. Sequential oxidation of organoboranes by anhydrous TMNO.⁷⁶

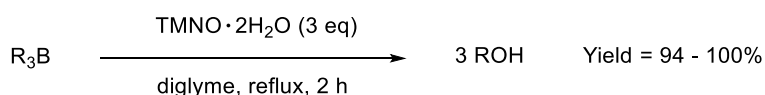
It has long been thought that TMNO promoted oxidations proceed with initial coordination of the *N*-oxide to the vacant p-orbital of the boron centre of alkylborane **48**. Subsequently, 1,2-alkyl migration occurs from the boron atom to the oxygen derived from the *N*-oxide, which generates the desired O-R bond (Scheme 31).^{75,78} This process can occur up to three times, with an equivalent of amine by-product being formed during each subsequent oxidation step.⁷⁵ Such a mechanism is reminiscent of the Baeyer-Villiger oxidation.⁷⁰



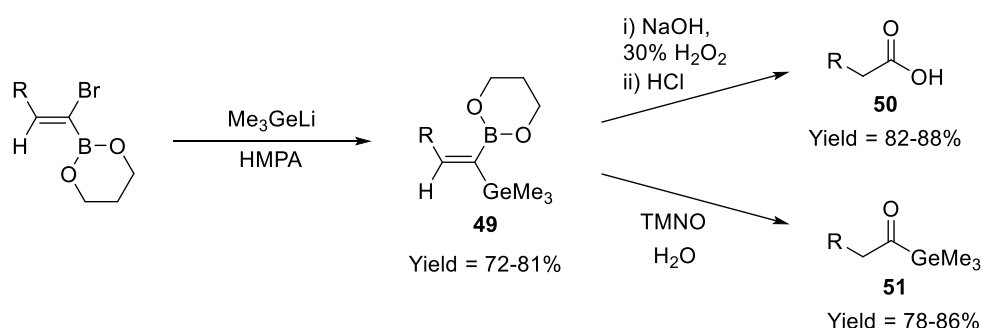
Scheme 31. Mechanism of organoborane oxidation by TMNO.⁷⁵

It has been shown by Kabalka *et al.* that direct oxidation of organoboranes to their alcohol products can be achieved *via* treatment of such species with commercially available trimethylamine *N*-oxide dihydrate at reflux (Scheme 32).^{76,77,79} Trimethylamine *N*-oxide is known to be a particularly mild oxidising agent, which exhibits superior functional group compatibility relative to sodium hydroxide/hydrogen peroxide oxidation conditions that are commonly

employed, thus reducing undesired side reactions.^{5,76,77,79} This is further exemplified within the oxidation of (*E*)-1-trimethylgermyl-1-alkenyl boronate esters **49** reported by Bhat and Varghese (Scheme 33).⁸⁰ Treatment of isolated intermediate **49** with an alkaline solution of hydrogen peroxide and subsequent acidification resulted in the formation of carboxylic acid species of the general form **50**, whilst oxidations performed with trimethylamine *N*-oxide saw retention of the germyl functionality and afforded alkyl trimethylgermyl ketones **51**.⁸⁰

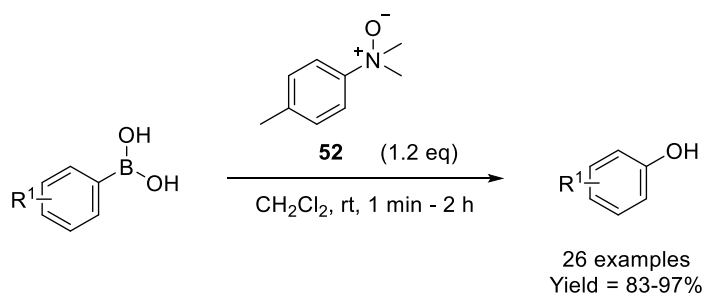


Scheme 32. Direct oxidation of organoboranes to alcohols using TMNO dihydrate.⁷⁹

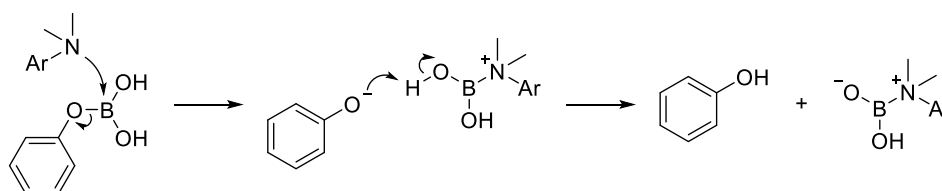


Scheme 33. Differing products from the oxidation of (*E*)-1-trimethylgermyl-1-alkenyl boronate esters **49** with i) alkaline hydrogen peroxide and ii) trimethylamine *N*-oxide.⁸⁰

In 2012 a room temperature procedure was developed for the direct hydroxylation of (hetero)aryl boronic acids and boronate esters using *N,N*-dimethyl-4-toluidine *N*-oxide (**52**) as the oxidant (Scheme 34).⁸¹ This mild methodology displayed exceptional functional group tolerance and was largely insensitive to the sterics and electronics of the arylboronic acid; generating the desired phenols in a matter of minutes (26 examples, 83-97%, ≤ 5 min).⁸¹ Notably, readily oxidisable functionalities, such as aldehydes, sulphides and olefins, remained intact.⁸¹ Additionally, aromatic *N*-oxide **52** mediated the oxidation of boronic acid derivatives, such as boronate esters, as well as challenging heteroaryl boronic acids to afford the corresponding phenols or carbonyl tautomers in good yield (9 examples, 63-92%, ≤ 2 hours).⁸¹ Liberation of the alcohol product in both of the aforementioned examples is proposed to occur *via* attack of the alkoxyborane species by the previously eliminated amine (Scheme 35).⁸¹

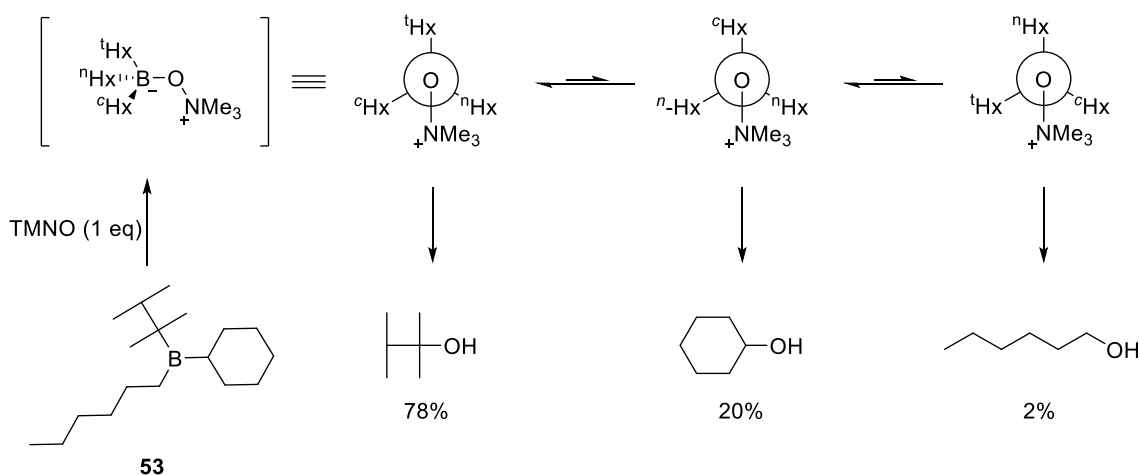


Scheme 34. Direct hydroxylation of (hetero)aryl boronic acids and boronate esters using *N,N*-dimethyl-4-toluidine *N*-oxide (**52**) as the oxidant.⁸¹



Scheme 35. Proposed mechanism for liberation of the alcohol from the alkoxyborane species.⁸¹

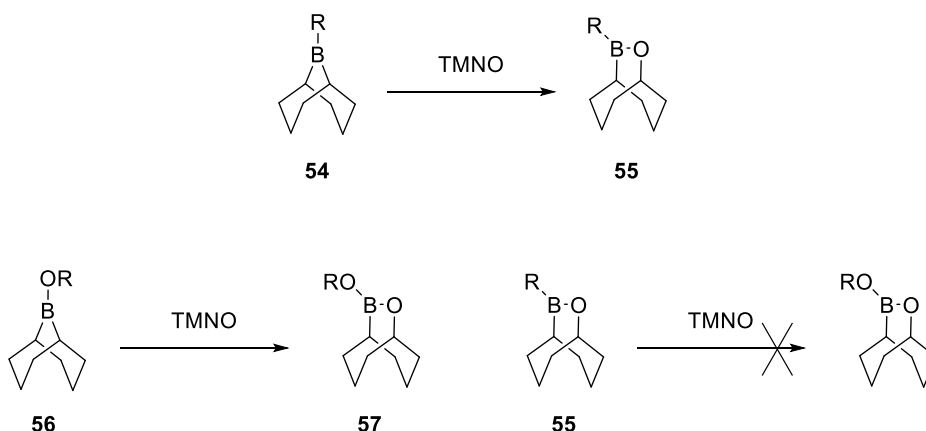
When unsymmetrical trialkylboranes (**53**) were treated with one equivalent of TMNO, the bulkiest groups were found to be more susceptible to oxidation (3° > 2° > 1°).^{76,78} As a rationale for this observation, Soderquist and Najafi proposed that during the elimination step an antiperiplanar alignment is adopted between the trimethylamine and the migrating group.^{76,78} Thus, within the most stable conformer of the 'ate' complex, the bulkiest substituent is orientated *anti* to the amine leaving group in order to minimise steric hindrance (Scheme 36).^{76,78}



Scheme 36. Selective migration of trialkylboranes using TMNO.⁷⁸

Alternatively, it was reported that the oxidation of cyclic species *B*-substituted 9-borabicyclo[3.3.1]nonane (9-BBN) **54** selectively provides borinate **55** as the sole product rather than as a mixture (Scheme 37).^{76,78} Additionally, whilst **56**, which is formed from alcoholysis of 9-BBN, can be further oxidised to **57**, the isomeric species **55** is almost completely

unreactive.^{76,78} According to Figure 5, it would be anticipated that antiperiplanar migration of the alkyl group is disfavoured due to increased steric interactions between the amine and ring system, which reflects the findings.^{76,78}



Scheme 37. Selective oxidation of 9-BBN derivatives with TMNO.^{76,78}

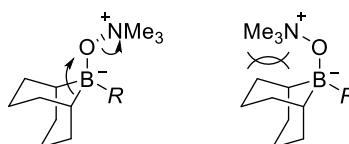


Figure 5. Steric argument demonstrating the preference for ring migration.^{76,78}

Preferential oxygen insertion within the ring was also observed for cyclic borinate derivative **58** but at a faster rate than **59** (Figure 6).^{76,78} Whilst this selectivity can be rationalised in the same manner, the rate increase can be attributed to the more favourable position adopted by the ^tBu group in species **58** relative to species **59**.^{76,78} In species **59** the boron atom is incorporated within two cyclohexyl rings and therefore the ^tBu group is required to simultaneously sit in both an axial and equatorial position, which is energetically unfavourable.^{76,78} Conversely, in species **58** the ^tBu group can adopt exclusively the equatorial position, which enhances the rate of the oxidation step.^{76,78}

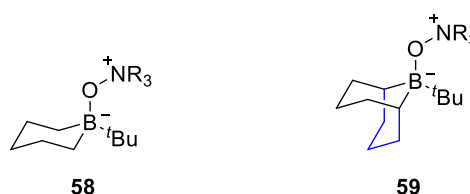
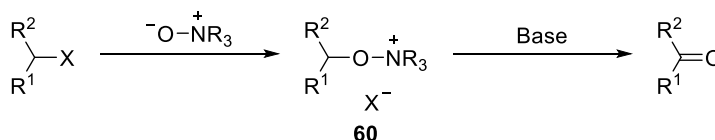


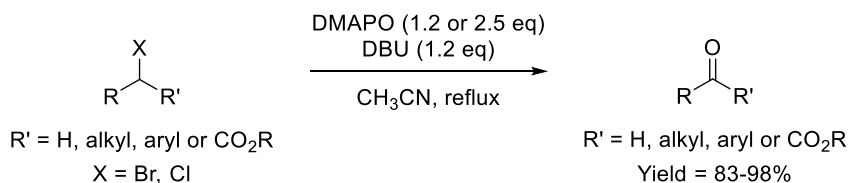
Figure 6. Cyclic boron – *N*-oxide complexes.⁷⁶

N-Oxides have also been employed within other oxidative transformations, such as the preparation of aldehydes and ketones from organic halides.⁸²⁻⁸⁶ Initially, the organic halide undergoes nucleophilic substitution with the *N*-oxide to generate *N*-alkoxy salt **60**, which may then undergo elimination to afford the desired carbonyl compound (Scheme 38).⁸⁴⁻⁸⁶ The elimination step is often base promoted, with careful selection required to ensure abstraction of the proton on the carbon α to the oxygen rather than β , which would otherwise generate an alkene.⁸⁴⁻⁸⁶



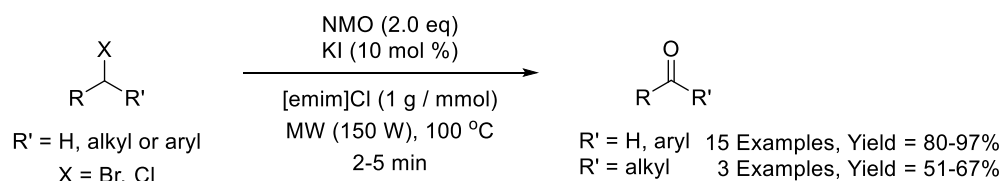
Scheme 38. Mechanism for the oxidation of organic halides with *N*-oxides.^{84,85}

For example, in 1981 Yamaguchi *et al.* reported that 4-dimethylaminopyridine *N*-oxide (DMAPO) could effectively oxidise primary benzylic and alkyl halides (X = Br, Cl) into the corresponding aldehydes in good to excellent yields (83-98%) by employing DBU as the base (Scheme 39).⁸⁵ Ketones were also accessed in excellent yields (98%) *via* the oxidation of secondary benzyl and acyclic alkyl bromides.⁸⁵ The authors determined that the use of a large excess of DMAPO (2.5 equiv.) facilitated extension of this methodology to the oxidation of α -bromo esters into α -keto esters (yield: 85-92%).⁸⁵



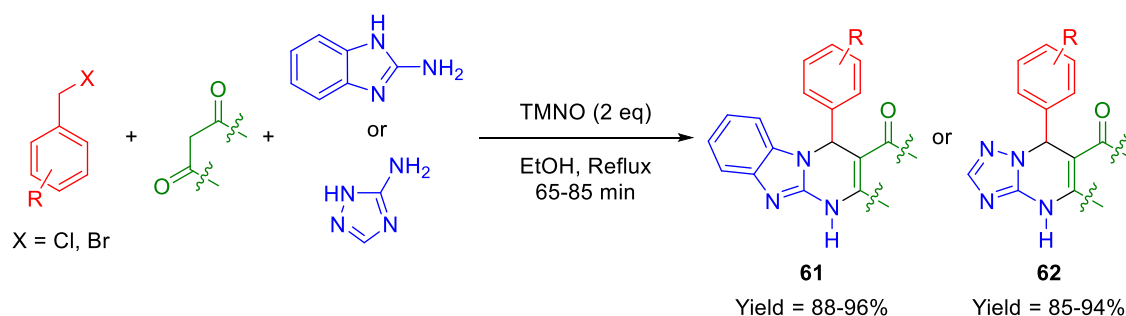
Scheme 39. 4-Dimethylaminopyridine *N*-oxide as an oxidising agent for organic halides.⁸⁵

Most recently an NMO mediated oxidation of organic halides in ionic liquids was developed by Pattarawarapan and co-workers, which is a microwave-assisted transformation (Scheme 40).⁸⁶ As observed with other methods, benzylic halides were the most reactive towards oxidation, with both bromo and chloro species of varying electronic demand successfully oxidised in excellent yields (83-97%) to the target aldehydes.⁸⁶ Primary and secondary bromides were also tolerated but those containing a β -proton gave compromised yields due to competing elimination reactions and in some instances hydrolysis.⁸⁶



Scheme 40. Microwave-assisted NMO oxidation of organic halides in ionic liquids.⁸⁶

In 2016, this *N*-oxide oxidation strategy was applied by Beerappa and Shivashankar to the one-pot synthesis of benzimidazolo/[1,2,4]triazolo quinazolinone derivatives (**61/62**) from the tandem reaction of benzyl halides (red) with an enol precursor (green) and an amino-substituted heterocycle (blue) using TMNO as the sole reagent (Scheme 41).⁸⁷ Initially, the benzyl halide is oxidised to generate the corresponding aldehyde *in situ* along with an equivalent of trimethylamine hydrogen halide, according to the process previously outlined in Scheme 38.⁸⁷ The liberated acid is then thought to promote the Knoevenagel condensation of the aldehyde with the *in situ* generated enol; affording a heterodiene, which upon 1,4-conjugate addition by the amine component, subsequent cyclisation and dehydration provides access to the relevant heterocyclic product.⁸⁷ Both electron rich and electron poor benzyl halides were amenable to this methodology and good to excellent yields of the quinazolinone derivatives were obtained irrespective of the electronics (85-96%).⁸⁷



Scheme 41. Application of the *N*-oxide promoted oxidation of benzyl halides to the synthesis of benzimidazolo/[1,2,4]triazolo quinazolinone derivatives.⁸⁷

1.4 *N*-Oxides as organocatalysts

1.4.1 Silicon chemistry

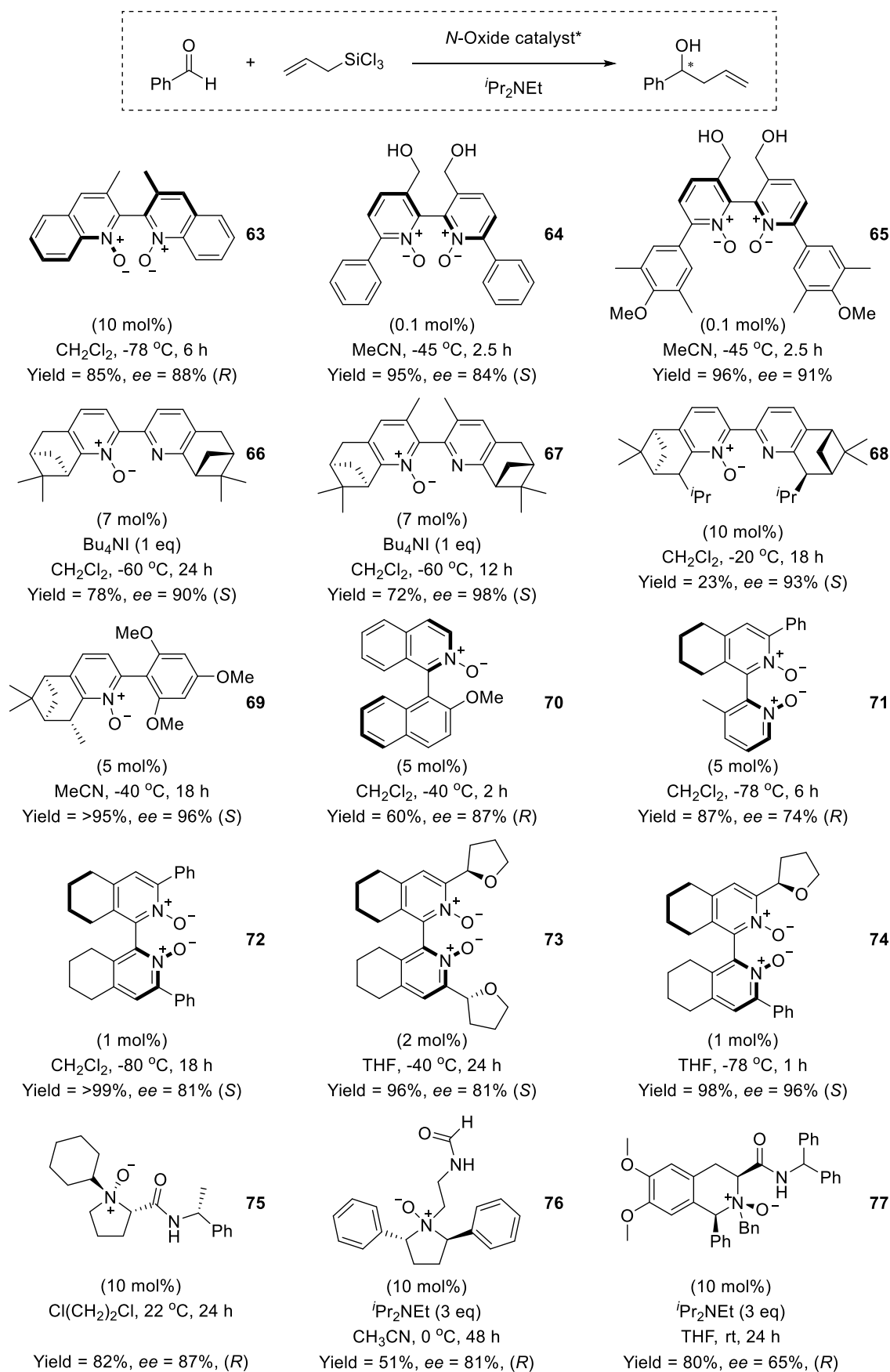
N-Oxides are classified as Lewis basic catalysts due to their ability to reversibly interact with a substrate *via* donation of an electron pair on their oxygen atoms.⁸⁸⁻⁹⁰ In this context, *N*-oxides have found widespread application within organosilicon chemistry; an area that has been extensively investigated and reviewed in recent years. Due to the high oxophilicity of silicon and the inherent nucleophilicity of *N*-oxides towards organosilicon reagents, *N*-oxides readily coordinate to tetravalent silicon.⁹⁰⁻⁹⁶ The resultant hypervalent silicate complex exhibits increased Lewis acidity due to the reduced electron density at the silicon centre and is therefore able to

activate electrophiles towards nucleophilic attack.^{90-92,97-100} Coordination of the *N*-oxide additionally enhances the electron density of substituents covalently bound to the silicon, resulting in the increased nucleophilicity of these groups.^{91,92} Both of these properties have been exploited within the transformations outlined below in sections 1.4.1.1 – 1.4.1.6.

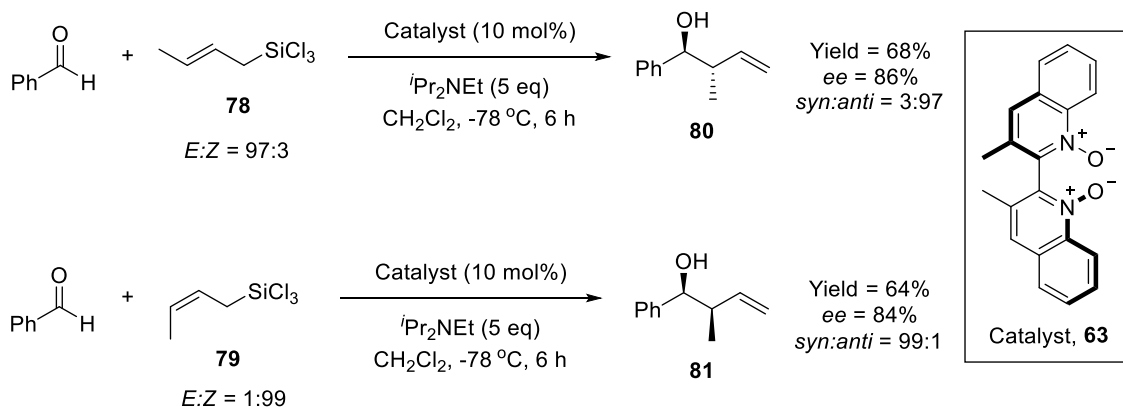
1.4.1.1 Allylation reactions

In 1998, Nakajima and co-workers reported the first example of an *N*-oxide catalysed enantioselective allylation reaction between an aldehyde and allyltrichlorosilane, as shown in Scheme 42.^{92-94,96,100,101} The developed C₂-symmetric catalyst **63** (Scheme 42), which is based on a biquinoline unit that possesses axial chirality, was found to afford good to high enantioselectivities for the addition of allyl groups to a range of substituted aromatic aldehydes bearing both electron-withdrawing and electron-donating functionalities (71-92% *ee*).^{90,92-94,96,100,101} Whilst this methodology was successfully applied to α,β -unsaturated aldehydes (80-81% *ee*), catalyst **63** was ineffective in controlling the enantioselectivity for allylation reactions of aliphatic aldehydes (7-28% *ee*).^{92,94,96,100} It was discovered that the rate of the reaction could be enhanced using a 5-fold excess of diisopropylethylamine, which the authors attribute to a ligand exchange process that liberates the active *N*-oxide species from the silylated product **84** (Scheme 44).^{92,94,96,100}

In order to probe the reaction mechanism, the allylation reaction between benzaldehyde and (*E*)- and (*Z*)-crotyltrichlorosilane (**78** and **79**) was investigated.^{90,93,94,96,102,103} As shown in Scheme 43, allylation reactions were found to proceed with extremely high diastereoselectivities, with the *E*-isomer **78** generating almost exclusively the *anti* diastereomer **80** and the *Z*-isomer **79** affording the *syn* configuration of the alcohol product **81**.^{90,93,94,96,101-103} Given this result, a 6-membered chair-like transition state **83** has been postulated for these allylation reactions, as shown in Scheme 44.^{90,93,94,96,102-105}



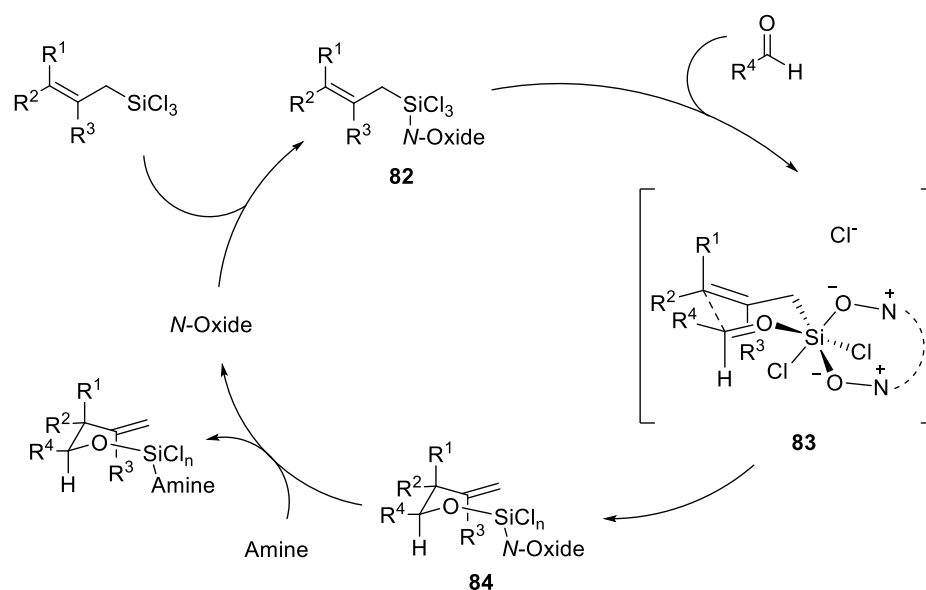
Scheme 42. Chiral N-oxide organocatalysts for the enantioselective allylation of benzaldehyde with allyltrichlorosilane.^{94,97-99,102,103,106-112}



Scheme 43. Allylation of benzaldehyde with *(E)*- and *(Z)*-crotyltrichlorosilane.^{94,102,103}

The proposed mechanism for *N*-oxide catalysed allylations is shown in Scheme 44, with the key elements as follows:^{90,94,96,102,103,106,107,113,114}

1. The *N*-oxide coordinates to the silicon of the allylsilane, creating hypervalent cationic silicate species **82** of increased Lewis acidity. It is thought that coordination of an *N*-oxide *trans* to the allyl group increases the nucleophilicity of the latter due to the strong sigma donating ability of the *N*-oxide.
2. The aldehyde is activated by coordination of its carbonyl group to the Lewis acidic silicon atom in a *cis* orientation relative to the allyl group.
3. Nucleophilic attack of the aldehyde by the activated allyl substituent generates the silicon bound homoallylic alcohol *via* the 6-membered, cyclic transition state **83**. Within this transition state, enantiodifferentiation is imparted by favourable 1,3-diaxial electrostatic interactions when both the C-H bonds (*i.e.* the aldehydic proton and where R³ = H) and the Si-Cl bond are aligned.^{115,116} Such a configuration is only produced during attack of a single face of the prochiral aldehyde.^{115,116}
4. The *N*-oxide is then liberated and rejoins the catalytic cycle.

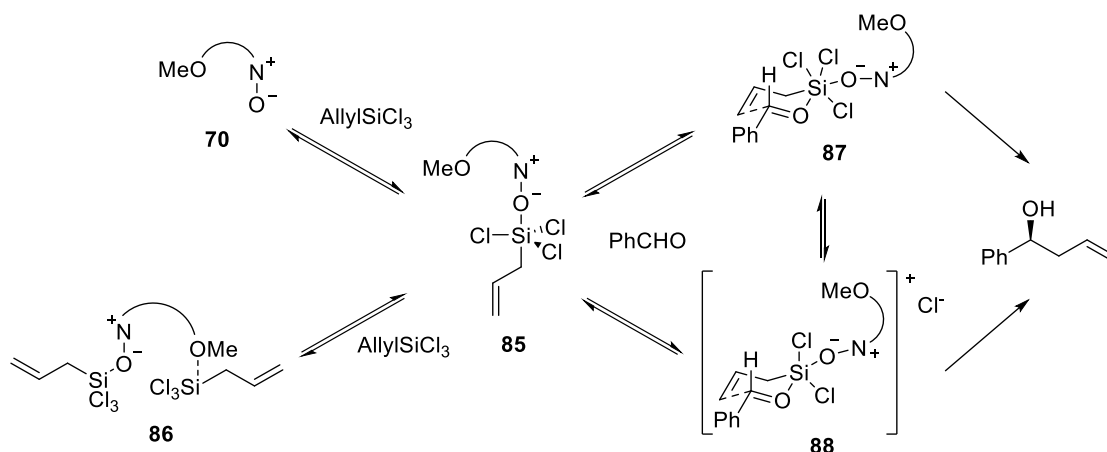


Scheme 44. Mechanism of *N*-oxide promoted allylation of aldehydes with allyltrichlorosilane.^{96,115,116}

Since this initial report, several examples of axially chiral mono and bis *N*-oxides derived from pyridine and other related *N*-heterocycles have been developed, with some representative examples displayed in Scheme 42 (**64**, **65**, **70-74**). The bipyridine based *N,N'*-dioxide **64** and its electron rich analogue **65**, which were developed by Hayashi *et al.*, display a comparable level of enantioselectivity to Nakajima's catalyst **63**.^{90,92,93,100,101,108,117} **64** and **65** also possess exceptional catalytic activity, with a typical catalyst loading of 0.1 mol% required for almost quantitative conversion of the aldehyde to the corresponding alcohol within 2.5 hours (*cf.* 6 hours for **63**).^{90,92,93,100,101,108,117} Therefore, these catalysts represent some of the most reactive *N*-oxides developed for this type of allylation reaction.^{90,93,101} However, *N,N'*-dioxide **64** has been shown to be particularly sensitive to the electronic demands of aryl-aldehyde substrates, with lower enantiomeric excess observed for substrates bearing electron withdrawing groups (e.g. *p*-CF₃: 56% *ee*).^{90,108,117}

As electron poor aldehydes commonly provide alcohols with reduced enantioselectivities relative to their electron rich counterparts, Malkov *et al.* focussed on designing a more effective catalyst for the asymmetric allylation of these substrates.^{90,101,109} In this regard, catalyst **70** was developed, which relies on favourable arene-arene interactions between the electron rich catalyst and electron deficient aldehyde.^{90,101,109} The reported trend in enantioselectivities is considered to be consistent with this proposal, with electron poor aldehydes affording alcohols in high enantiomeric excess (89-96% *ee*), whilst electron rich aldehydes provided essentially racemic homoallylic alcohols (0-12% *ee*).^{90,101,109}

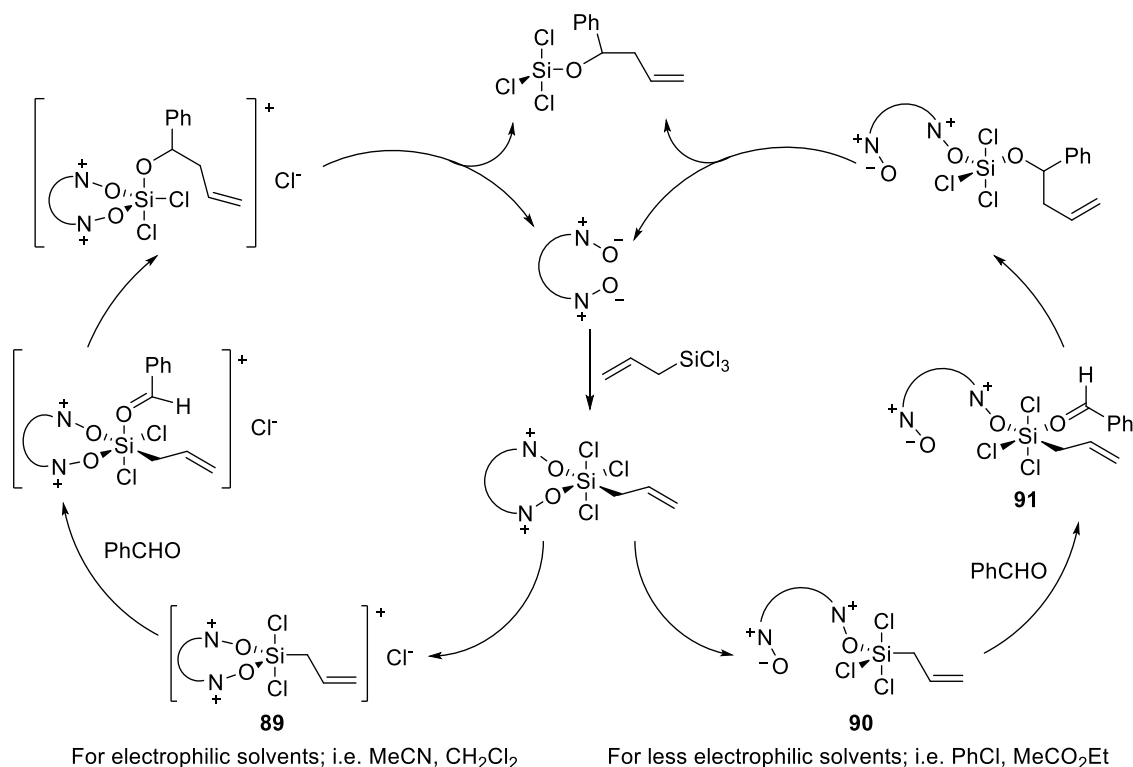
After extensive mechanistic studies, Malkov and co-workers have proposed the reaction pathway shown in Scheme 45 for allylation reactions catalysed by *N*-oxide **70**.⁸⁹ From the reaction kinetics, it has been elucidated that the reaction is first order with respect to catalyst; suggesting coordination of a single *N*-oxide to form intermediate **85**.⁸⁹ Although the reaction was also found to be first order in allyltrichlorosilane up to a silane:catalyst ratio of 15:1, at higher concentrations the order in silane becomes negative.⁸⁹ This was attributed to the formation of catalytically inactive species **86**, which requires dissociation of the methoxy bound allylsilane before **85** can re-enter the catalytic pathway.⁸⁹ It has been proposed that the final reaction step may occur *via* either an associative or dissociative process, with octahedral and trigonal bipyramidal transition states respectively (**87** and **88**).^{89,114} Due to increased steric crowding about the silicon, reactions proceeding *via* transition state **87** are predicted to generate superior enantioselectivities, which was reflected in the high stereochemical induction afforded by catalyst **70** for electron deficient aldehydes.^{89,114} Additionally these results were obtained in non-polar solvents, which would poorly stabilise transition state **88**, and is therefore suggestive of the reaction proceeding *via* an associative pathway.^{89,114}



Scheme 45. Proposed mechanistic pathways for *N*-oxide catalyst **70**.⁸⁹

Whilst these results suggest a dependency of the enantioselectivity and reactivity on the solvent employed, a comprehensive study into solvent effects wasn't performed until 2009 by Kotora and co-workers.^{89,118} For catalyst systems **72-74**, it was observed that the nature of the solvent influenced the degree and sense of enantioselectivity, with a variation in the enantiodifferentiating transition states proposed as a rationale for this trend.^{110,118-120} This was evidenced by the results of a conductivity study.¹¹⁸ A mixture of (*S*)-*N*-oxide **72** with the allylsilane was shown to give higher conductivities relative to the individual components in acetonitrile or dichloromethane, which are known to afford an (*R*)-alcohol, whilst this phenomenon was not observed for chlorobenzene or ethyl acetate, which both yield the corresponding (*S*)-enantiomer.¹¹⁸ It is believed that more electrophilic solvents favour formation of the penta-coordinated cationic

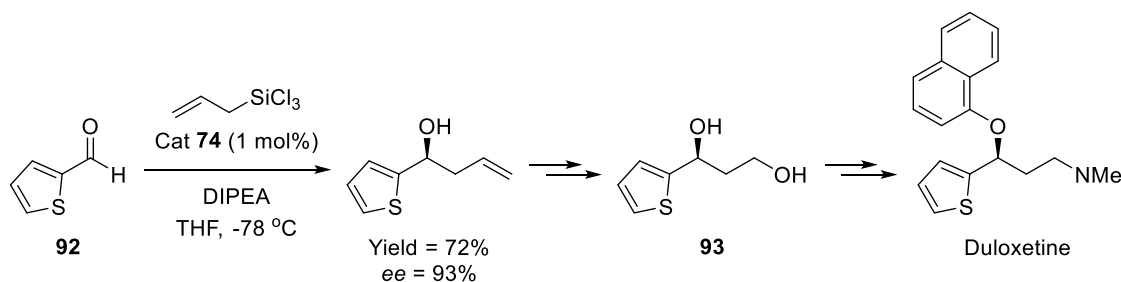
complex **89**, as shown in Scheme 46, with the impetus for dissociation being the ability of these solvents to solvate the chloride anion.¹¹⁸ However, in less electrophilic solvents, namely chlorobenzene or ethyl acetate, this solvation effect is reduced and the reaction proceeds *via* the neutral pathway.¹¹⁸ In this case, the *N*-oxide binding mode switches from bidentate to monodentate to provide a free coordination site for the carbonyl functionality, as shown in intermediate **90**.¹¹⁸ Although these solvent effects may be expected for other *N*-oxides, extension of this methodology to explain the outcome of other systems has not yet been demonstrated.



Scheme 46. Effect of solvent on the mechanistic pathway for *N*-oxide catalyst **72**.¹¹⁸

Tetrahydrofuran was found to be the most effective solvent for asymmetric allylations catalysed by *N*-oxides **72-74**.^{110,111,118,120,121} The high levels of enantioselectivity achieved are consistent with the more tightly packed transition state **91** of the neutral pathway.^{110,111,118,120,121} Of the three catalysts, **74** typically gave the highest levels of asymmetric induction, which has been attributed to its unsymmetrical nature resulting in one *N*-oxide moiety being more labile and therefore more capable of generating intermediate **90**.^{110,111,118,120,121} Specifically, enantioselectivities of up to 96% *ee* and 99% *ee* were achieved for aromatic and α,β -unsaturated aldehydes respectively.^{110,111,118,120,121} More recently, Kotora and co-workers have examined the catalytic potential of **74** for the allylation (and crotylation) of otherwise largely under researched substrate classes, such as β -haloacrylaldehydes and *o*-substituted benzaldehydes, as well as the synthetic applicability of the developed methodology.¹²²⁻¹²⁴ For instance, the enantioselective allylation of thiophene-2-carbaldehyde (**92**) was identified as a key step in the synthesis of diol **93**, which is a

precursor to the antidepressant Duloxetine (Scheme 47).¹²⁴ *N,N'*-Dioxide **74** promoted the allylation in high yield and excellent enantioselectivity, with the chiral purity successfully retained within diol **93**.¹²⁴



Scheme 47. Enantioselective allylation of thiophene-2-carbaldehyde (**92**) catalysed by *N,N'*-dioxide **74** as the first step in the synthesis of Duloxetine.¹²⁴

Terpene-derived bipyridine *N*-oxides **66–69** represent a further class of chiral catalysts developed for the synthesis of optically active homoallylic alcohols from the reaction of aldehydes with allyltrichlorosilane.^{91–93,101,103,104,106,107,112–114} Within these systems, stereochemical control primarily originates from the 2,2'-bipyridyl chiral axis, which was determined from the observation that atropisomers **94** and **95** provided the opposite sense of enantioinduction (Figure 7).^{106,107,114} For uncomplexed catalysts **66** and **68**, with free rotation about the aryl-aryl bond, the chiral twist is created upon chelation to the silicon and the configuration adopted is influenced by the chirality of the terpenoid backbone.^{107,114}

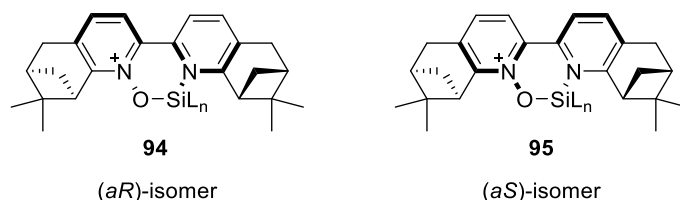
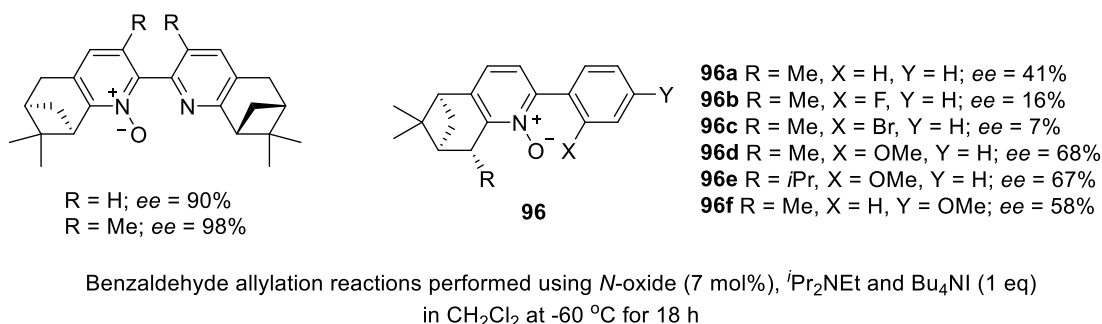


Figure 7. Atropisomers of PINDOX (catalyst **66**).¹⁰⁷

In 2002, Malkov and Kocovsky were the first to report on the synthesis and activity of a series of terpene-derived *N*-monooxides: PINDOX **66**, Me₂PINDOX **67** and *iso*-PINDOX **68** (Scheme 42).^{92,93,101,106,107,113} These structurally related catalysts were found to exhibit superior enantioselectivities relative to *N,N'*-dioxide **63**, however the rate of the reaction was compromised and reaction times between 18 and 24 hours were typically required.^{92,93,101,106,107,113} The exceptionally high enantioselectivity observed for **67** was attributed to restricted rotation about the bipyridyl-backbone, which arises from the incorporated methyl groups.^{92,93,101,106,107,113} This rigidity results in the axial chirality of the catalyst being determined prior to its chelation to silicon.^{92,93,101,106,107,113} However, the barrier to rotation is not sufficient to prevent isomerisation occurring in solution over extended periods of time.^{92,93,101,106,107,113} The resultant erosion of

stereoselectivity, in conjunction with the challenges associated with the synthesis of this catalyst, has led to Me₂PINDOX **67** finding limited application.^{92,93,101,106,107,113} Conversely, PINDOX **66** and *iso*-PINDOX **68** have been applied to a range of aromatic aldehydes, with the enantioselectivity being largely unaffected by electronic variations within the substrate (65-98% *ee* and 85-97% *ee* using **66** and **68** respectively).^{92,93,101,106,107,113}

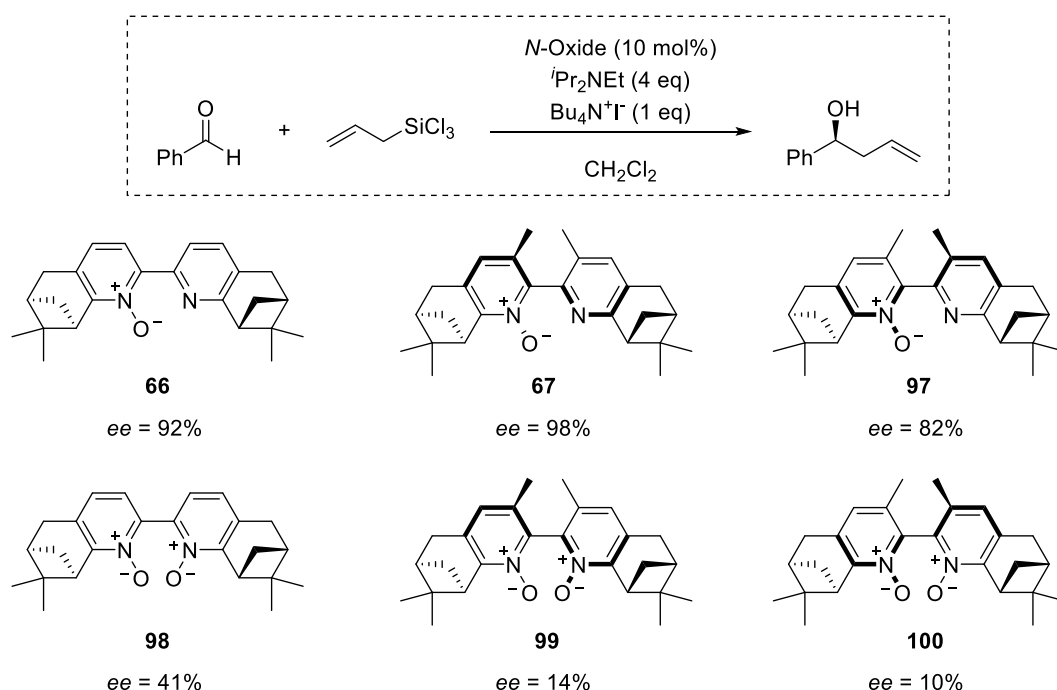
It is interesting to note that, whilst the high stereoselectivity observed for the PINDOX series is believed to be derived from *N*-*O*-chelation to the silicon, the extent of asymmetric induction achieved by mono-pyridine analogues is thought to be primarily related to the electronics of the catalyst's aryl ring.^{91,101,107,112,114} Whilst investigating the effect of varying the *ortho* substituent of **96**, Malkov *et al.* observed that the potentially chelating methoxy group induced the highest level of enantioselectivity (**96d** 68% *ee*) within the allylation reaction (Scheme 48).^{112,113} However, the *o*-fluoro-derivative **96b**, which also has a strong affinity for silicon, was found to be unsuccessful at controlling the stereoselectivity of this allylation reaction (16% *ee*).^{103,112-114} This result, coupled with the comparatively high *ee* achieved for the unsubstituted analogue **96a** (41% *ee*), is indicative of an electronic effect, rather than chelation, being the major factor influencing the stereoselectivity.¹¹²⁻¹¹⁴ This was further evidenced by the modest enantioselectivity achieved by the *para*-methoxy isomer **96f** (58% *ee*), which is unable to chelate.¹¹²⁻¹¹⁴ It has been postulated that higher levels of electron density over the biaryl unit (F → H → OMe) results in greater arene-arene interactions, in the form of π -stacking, between the aryl ring of the catalyst and the electrophile; resulting in higher selectivity and reactivity.¹¹²⁻¹¹⁴ With this knowledge in hand, the more electron rich monopyrindine *N*-oxide METHOX **69** was designed (Scheme 42), which was found to afford high enantioselectivities and yields for all reactions including those run at room temperature.¹¹²



Scheme 48. Influence of the electronics of **96** on the *ee* achieved for the allylation of benzaldehyde.^{112,113}

Intriguingly, the allylation of benzaldehyde catalysed by *N,N'*-dioxides **98**, **99** and **100** gave very poor asymmetric induction relative to the related *N*-monooxides **66**, **67** and **97** respectively (Scheme 49).¹⁰⁷ As the same transition state is assumed for both catalyst classes, Chelucci *et al.*

have attributed this discrepancy to the chelate ring size and therefore ligand bite angle around the central silicon atom (Figure 8).^{91,104} In order to examine the effect of chelate ring size on the reaction, Chelucci *et al.* synthesized the structurally related *N*-oxides **101** and **102**, which incorporate an isopropylidene backbone, and investigated their ability to function as catalysts for this allylation reaction (Scheme 50).^{91,104} In contrast to bipyridine *N*-monooxide **66** (87% *ee* at -40 °C), the bipyridylmethane *N*-monooxide **101** was essentially ineffective at -40 °C.^{91,104} However, bipyridylmethane *N,N'*-dioxide **102** exhibited much higher enantiocontrol than its bipyridine analogue **98** (85% *ee* at -40 °C vs 41% *ee* at -90 °C) and achieved similar selectivity to *N*-monooxide **66**.^{91,104} Therefore, Chelucci concluded that ligands creating an even-membered ring upon chelation to the silicon ($n = 3$, $m = 2$) induce higher levels of stereochemical control due to their bite angles permitting superior chirality transfer (Figure 8).^{91,104}



Scheme 49. A comparison of enantioselectivities achieved using bipyridine mono- and dioxides for the allylation of benzaldehyde.¹⁰⁷

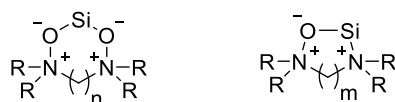
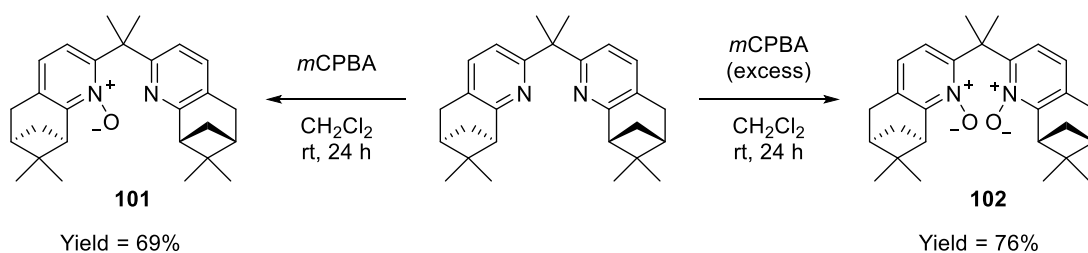
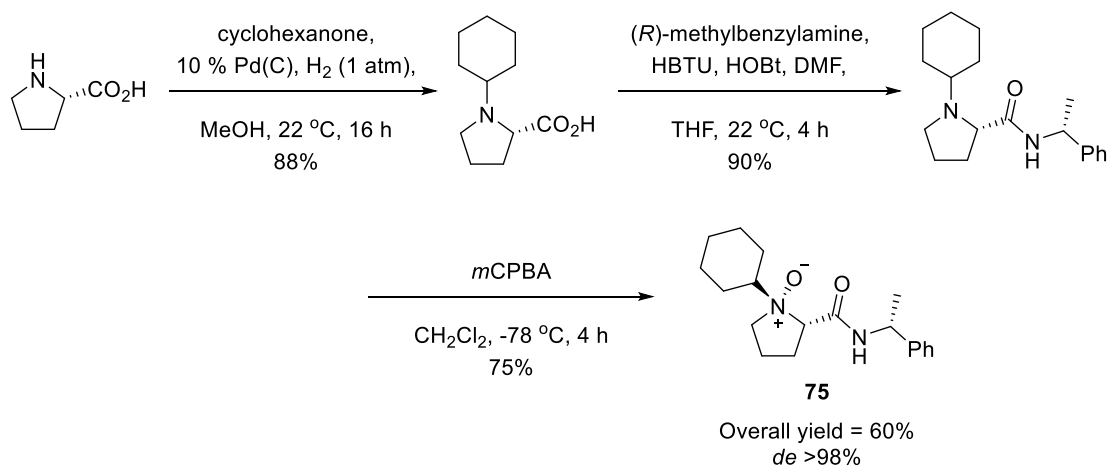


Figure 8. Chelate ring size model.¹⁰⁴

Scheme 50. Synthesis of dipyridylmethane derived *N*-oxides.¹⁰⁴

Hoveyda *et al.* were the first to identify an aliphatic tertiary *N*-oxide which could successfully catalyse the enantioselective allylation of aldehydes.^{92,97,98,103} Unlike many of its predecessors, the preparation of **75** did not involve a lengthy synthesis, modifications or kinetic resolution.^{97,98,103,125} Instead, this proline derived *N*-oxide was synthesized in three steps from commercially available L-proline in 60% overall isolated yield, with recrystallisation of the desired catalyst constituting the only purification required (Scheme 51).¹⁰³

Scheme 51. Synthesis of proline derived *N*-oxide **75**.¹⁰³

As previously observed for other *N*-oxides, allylation reactions are believed to proceed *via* a 6-membered cyclic transition state, as shown in Figure 9, with *N*-oxide **75** coordinated to the silicon in a bidentate fashion through the oxygen atoms of its *N*-oxide and amide carbonyl.¹⁰³ It has been postulated that the *trans* configuration of the electron withdrawing amide carbonyl and aldehyde results in activation of the latter towards nucleophilic attack.¹⁰³ Although the enantioselectivities achieved and reaction times required weren't superior to many of the other *N*-oxide catalysts shown in Scheme 42, it was possible to conduct the reaction at room temperature, which quite dramatically increases the potential industrial applicability of this methodology.¹⁰³

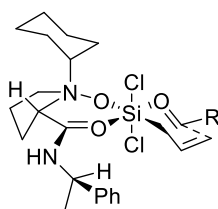


Figure 9. 6-Membered transition state for allylation reactions catalysed by **75**.¹⁰³

Subsequent to the development of this catalyst, two more examples of sp^3 hybridised aliphatic *N*-oxides have emerged within the literature (**76** and **77**), which can also be simply prepared in four steps or less and their allylation reactions carried out at or above 0 °C.^{97,98} Benaglia and co-workers investigated a series of amine *N*-monooxides based on a *trans*-2,5-diphenylpyrrolidine skeleton, with the most active being **76**, as shown in Scheme 42.⁹⁷ Structurally, the catalyst is conformationally rigid and incorporates two stereogenic centres adjacent to the active site.⁹⁷ In contrast to **75**, the nitrogen atom is chirotopic rather than stereogenic.⁹⁷ It was determined that functionalising the *N*-alkyl chain with a chelating group was a prerequisite for achieving good stereocontrol and that a 5 atom spacer between the *N*-oxide and carbonyl coordinating elements was optimal in these allylation reactions for activity and chiral induction.⁹⁷ The favourable formation of an eight-membered chelate is consistent with the model proposed by Chelucci.^{91,97,104} Unusually, this catalyst induces good levels of stereochemical control for the enantioselective addition of allylchlorosilanes to aliphatic aldehydes (81-85% *ee*) as well as aromatic aldehydes (55-81% *ee*).⁹⁷ Nevertheless, reaction times were extremely long (48 hours) and many of the yields reported were quite low (23-71%).⁹⁷

Interestingly, catalyst **77**, which was recently reported by Govender *et al.*, affords the opposite sense of stereochemical induction for sterically demanding aldehydes relative to smaller species, with a reversal of stereochemistry (*R* to *S*) being observed as the sterics of the group was increased.⁹⁸ The authors postulate that this observation provides evidence for the chiral pocket, created by the bulky diphenyl group, surrounding the aldehyde prior to nucleophilic attack by the allyl group.⁹⁸ Whilst good yields of alcohols were typically achieved in the presence of **77** (50-93%), only modest enantioselectivities were observed for aryl aldehydes (51-65% *ee*).⁹⁸

Several other novel catalysts have also been developed for the enantioselective allylation of aldehydes (**103-109**), as summarised in Figure 10, with the aim in many cases of achieving straightforward catalyst synthesis or catalyst recovery.¹²⁵⁻¹³³ However, in some instances these catalyst systems afford inferior enantioselectivities relative to those *N*-oxides shown in Scheme 42.¹²⁵⁻¹³³ Interestingly, the electron rich, conformationally rigid pyridine *N*-oxide **109** provided

superior enantioselectivities for electron rich benzaldehyde derivatives relative to the electron deficient congeners, which is in contrast to catalyst **70**.¹³³

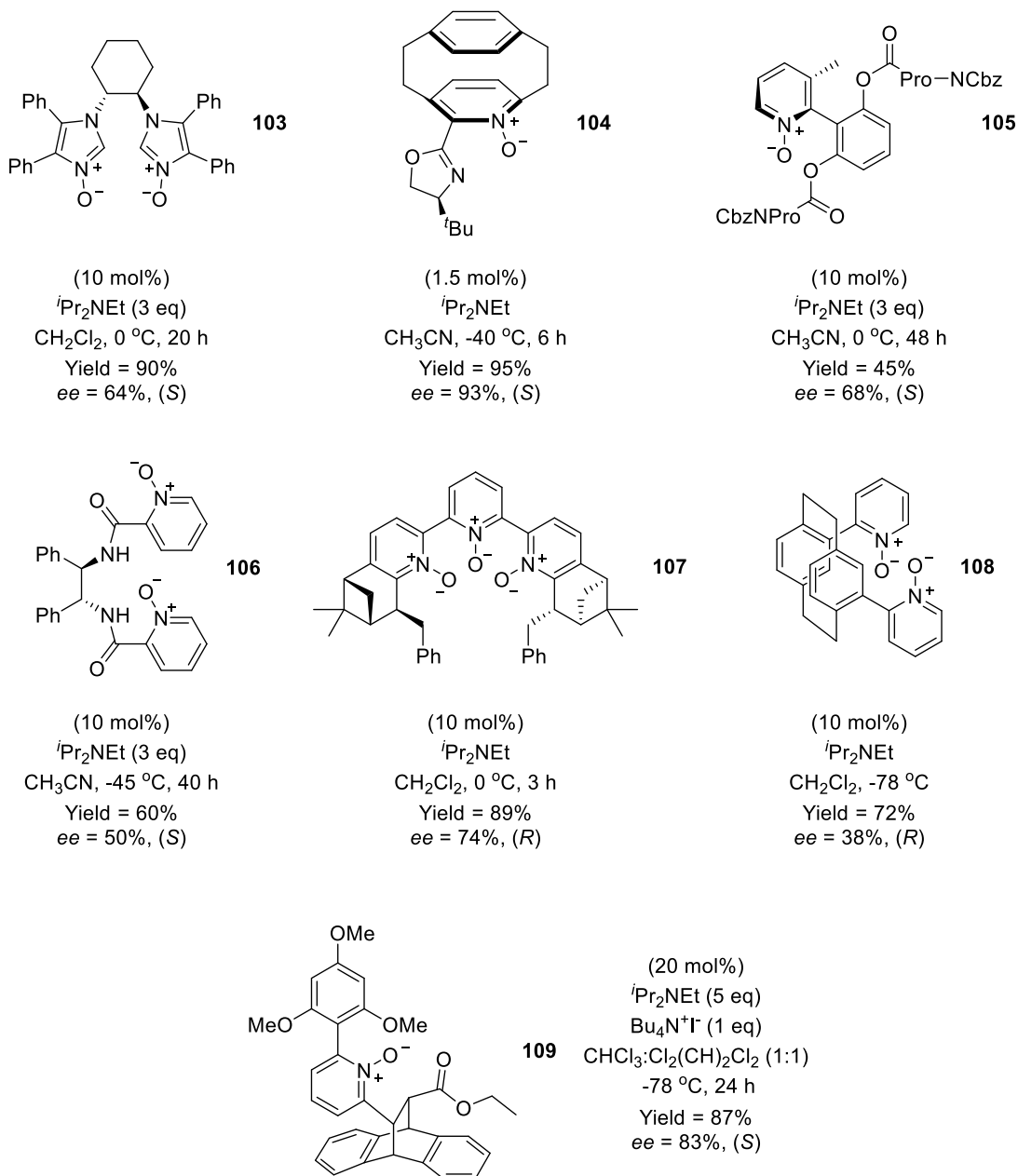


Figure 10. Alternative *N*-oxide catalysts investigated for the allylation of aldehydes, with values given for the allylation of benzaldehyde.^{125-129,131,133}

Most recently, Zhu and co-workers have developed a series of axially chiral 1,1'-biscarboline *N,N'*-dioxides **110-114** for the enantioselective allylation of aldehydes (Figure 11).¹³⁴⁻¹³⁷ With a catalyst loading of just 1 mol%, methyl and isopropyl ester derivatives **110** and **111** were found to impart extremely high levels of enantioselectivity within the reaction of aromatic, heteroaromatic, α,β -unsaturated and more significantly aliphatic aldehydes (**110**: 53-90% yield, 91-99% *ee*; **111**: 50-92% yield, 88-99% *ee*).^{134,135} Both catalysts exhibited previously unprecedented levels of stereochemical control for the formation of enantioenriched homoallylic

alcohols from aliphatic aldehydes (92-97% *ee*).^{134,135} Isopropyl ester derivative **111** was also successfully applied to the analogous crotylation reactions, with absolute diastereoselectivity and high enantioselectivities reported (80-96% *ee*).¹³⁵ It was found that substitution of the ester functionality for an amide (**113**) resulted in a reversal of the enantiofacial selectivity; generating the (*R*)-enantiomer instead of the (*S*)-enantiomer of the product.¹³⁶ This reversal in configuration has been attributed to the disparate binding modes of the *N,N'*-dioxide catalyst in the transition states (Figure 12).¹³⁶ Within ester **110** the two oxygens of the *N*-oxide are close in space, allowing for the catalyst to bind to the silicon as a bidentate oxodonor (**116**), as is commonly observed.¹³⁶ Alternatively, the oxygens of the two *N*-oxide moieties are forced apart within amide analogue **113**, which results in chelation to two distinct silyl species (**115**).¹³⁶ Upon coordination of the two silicon centres, the amide may change configuration leading to a transition state in which attack of the alternate face of the aldehyde is preferred.¹³⁶ In accordance with this hypothesis, ester functionalised mono *N*-oxide **117** provided the (*R*)-enantiomer of the product, as observed with amide catalyst **113**.¹³⁶ Amide functionalised *N,N'*-dioxides were also found to promote the allylation of a range of aromatic aldehydes in good enantioselectivities, with superior results in this case achieved employing cyclic derivatives, such as **113** (80-97% yield, 67-96% *ee*).¹³⁶ Interestingly, greatly compromised enantiocontrol was observed for allylations performed with structurally related ether species of the general form **114**, highlighting the importance of the carbonyl moiety.¹³⁵

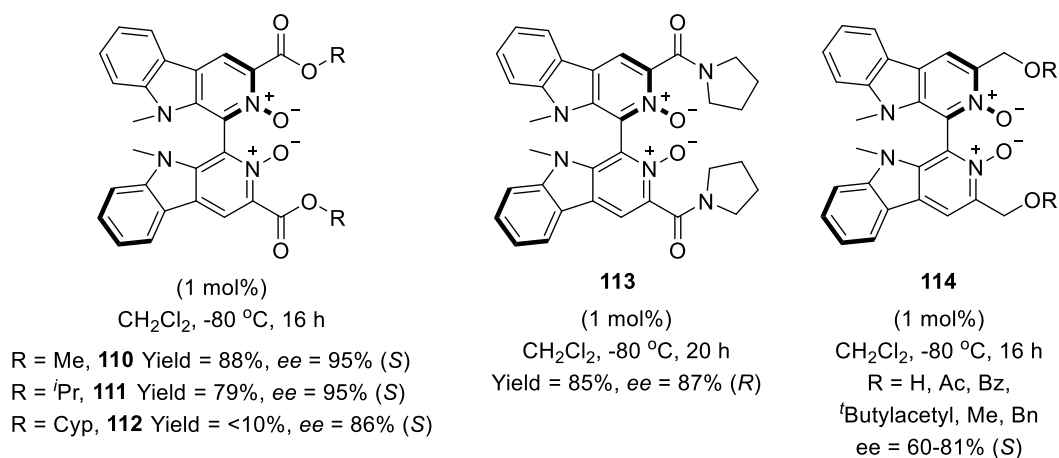


Figure 11. Axially chiral 1,1'-biscarboline *N,N'*-dioxides **110-114** developed for the enantioselective allylation of aldehydes.¹³⁴⁻¹³⁷

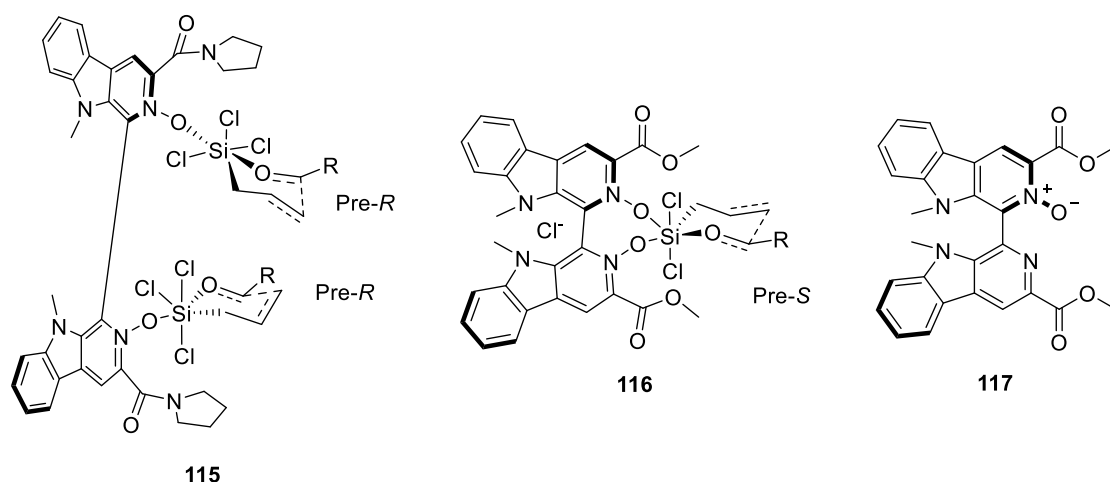
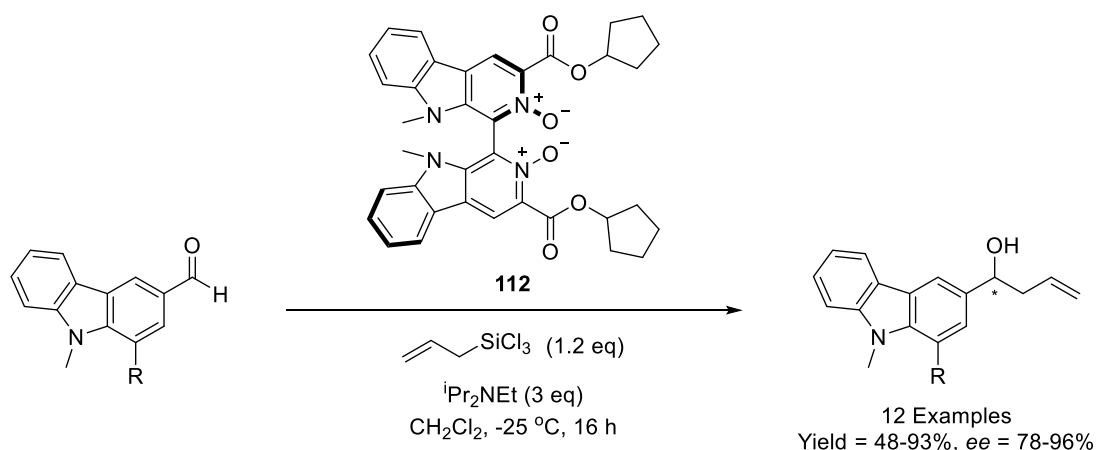


Figure 12. Proposed transition states accounting for the reversal of enantiofacial selectivity within allylation reactions catalysed by ester and amide substituted derivatives 110 and 113.¹³⁶

Typically, it is difficult to achieve high levels of enantioselectivity for larger substrates and many of the published methods have been restricted to simple substituted benzaldehydes.¹³⁷ To address this, bulky cyclopentyl ester derivative **112** was developed by Zhu *et al.* and was successfully applied to the allylation of a series of more elaborate aldehydes; generating the corresponding homoallylic alcohols in moderate to excellent yields and good enantioselectivities (Scheme 52).¹³⁷ Owing to the reduced reactivity of the larger substrates, the reactions could be performed at -25 °C without eroding the stereoselectivity obtained.¹³⁷

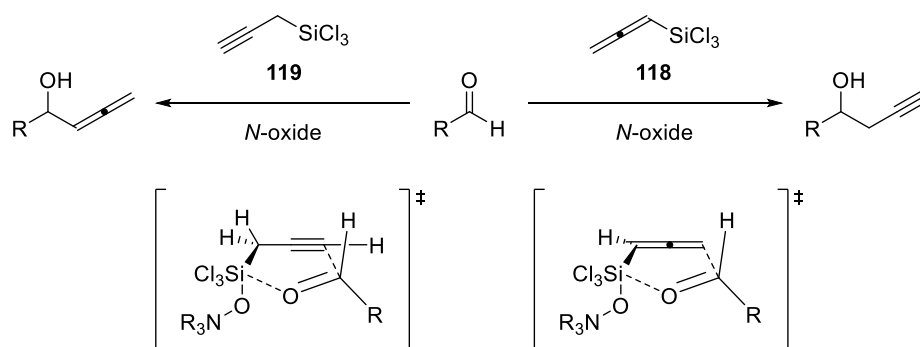


Scheme 52. Allylation of more elaborate aldehydes catalysed by biscarboline N,N' -dioxide derivative **112**.¹³⁷

1.4.1.2 Propargylation and allenylation reactions

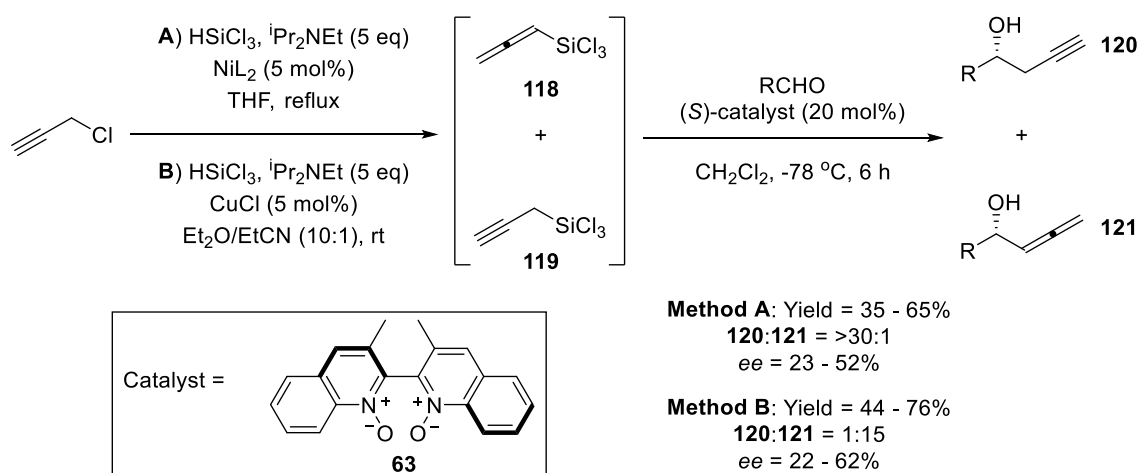
The N -oxide promoted propargylation and allenylation of aldehydes, using allenyl trichlorosilane **118** and propargyl trichlorosilane **119** respectively, proceeds in the same manner as detailed in section 1.4.1.1 for the allylation reactions; with the reactions occurring *via* the cyclic 6-membered

transition state shown in Scheme 53.^{90,92,93,138} However, this area of research is still very much in its infancy.



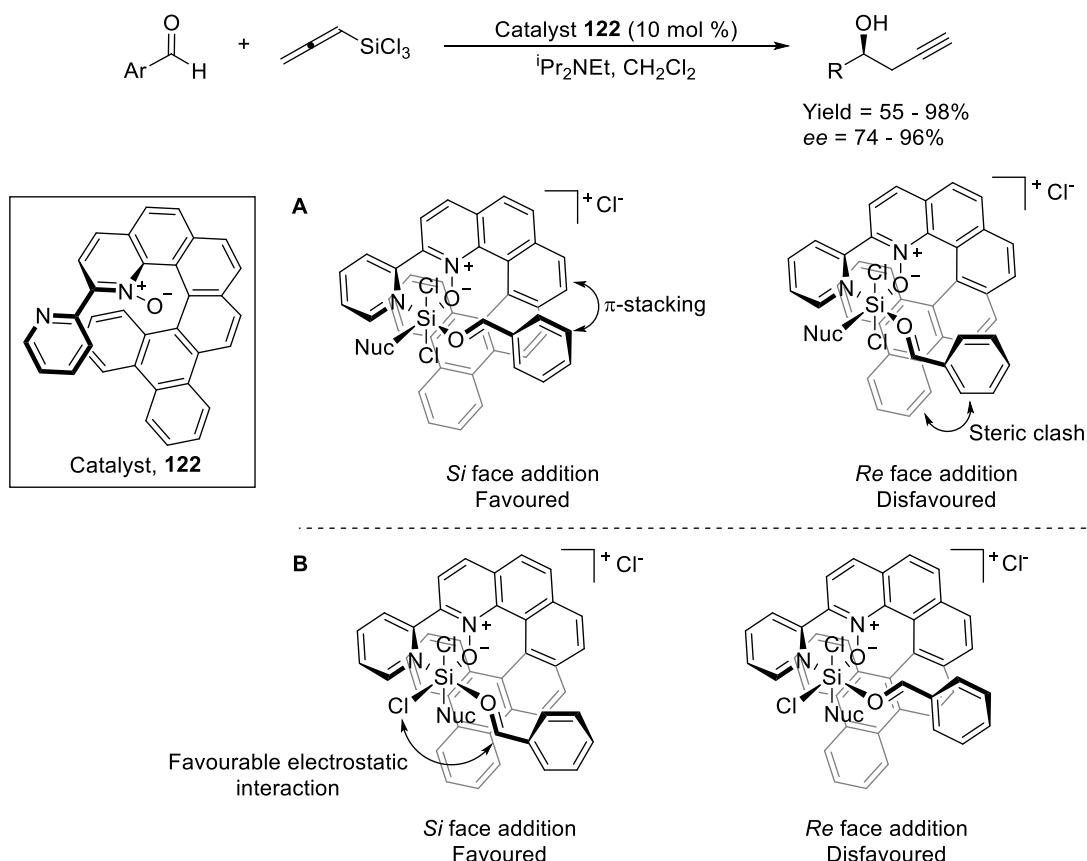
Scheme 53. *N*-Oxide promoted propargylation and allenylation reactions of aldehydes.^{93,139}

In 2002 Nakajima and co-workers were the first to demonstrate that chiral *N*-oxide catalysts could be employed in these reactions to afford enantiomerically enriched homopropargylic and allenic alcohols **120** and **121** respectively, which represent important classes of synthetically useful chiral intermediates for organic synthesis (Scheme 54).^{140,141} Specifically, axially chiral *N,N'*-dioxide **63** was employed as the catalytic additive and the required silane **118** or **119** was generated from propargyl chloride *in situ*.^{90,139,140} Although these reactions were found to proceed with relatively high regioselectivities with respect to the identity of the alcohol product formed (**120** or **121**), only moderate enantioselectivities were achieved, which are much reduced relative to the analogous allylation reaction.^{90,139,140,142,143} This observation has been attributed to the small energy difference between the *R* and *S* transition state configurations within the former, which is a result of the absent C-H bond β to the silicon that would otherwise provide enhanced enantiodiscrimination.^{115,116} Additionally, extension of the developed methodology to an aliphatic aldehyde provided diminished yields and enantioselectivities; reflecting the findings reported for the allylation of aldehydes promoted by *N*-oxide **63**.^{90,140}



Scheme 54. Propargylation and allenylation reactions of aldehydes promoted by *N,N'*-dioxide **63**.¹⁴⁰

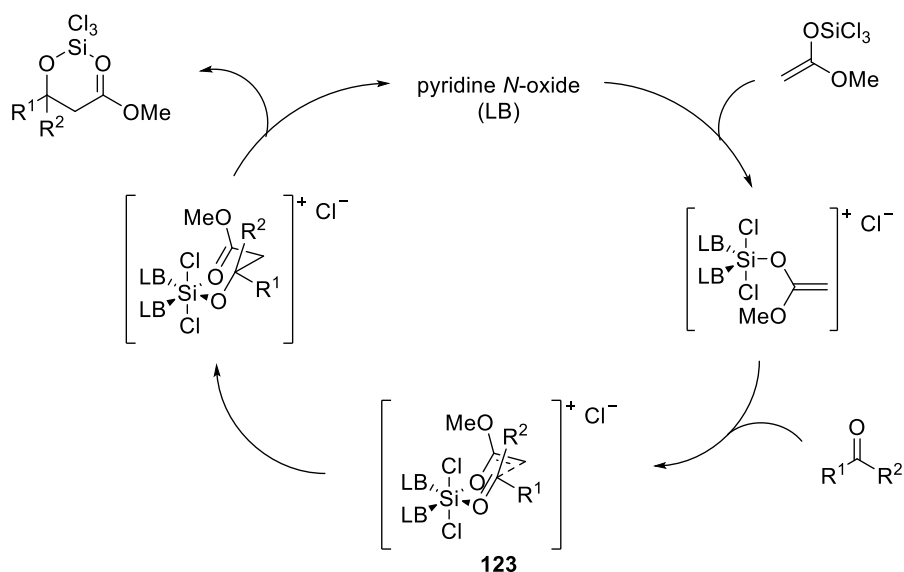
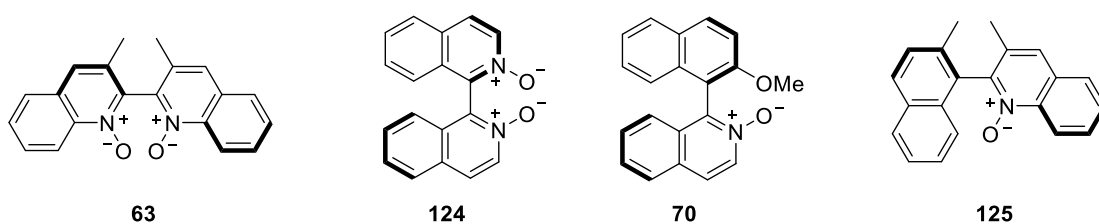
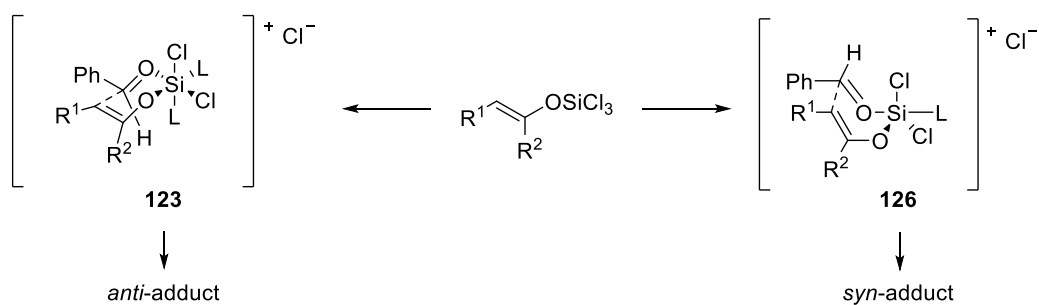
More recently, Takenaka *et al.* have reported that helically chiral *N*-oxide **122** generated (*S*)-homopropargylic alcohols in high enantioselectivities (74-96% ee) via the propargylation of aromatic aldehydes (Scheme 55, A).^{138,141} The authors proposed that the π - π interactions permissible between the aryl group of the aldehyde and the helicene backbone of the *N*-oxide rendered the addition of the nucleophile to the *Si* face of the aldehyde more favourable.^{138,141} Additionally, steric repulsions existing between the aldehyde and terminal benzo moieties of the catalyst in the transition state for *Re* face addition is believed to disfavour formation of the (*R*)-enantiomer.^{138,141} Based on the results of molecular modelling studies, Wheeler and co-workers have instead rationalised the observed enantioselectivity based on the favourable electrostatic interactions formed between the carbonyl carbon of the aldehyde and the silicon-bound chlorine in the transition state for *Si* face addition rather than π - π stacking (Scheme 55, B).^{138,141} Additionally, these results also supported the proposal that the chlorine ligands are *cis*-orientated in the transition state.^{138,141}



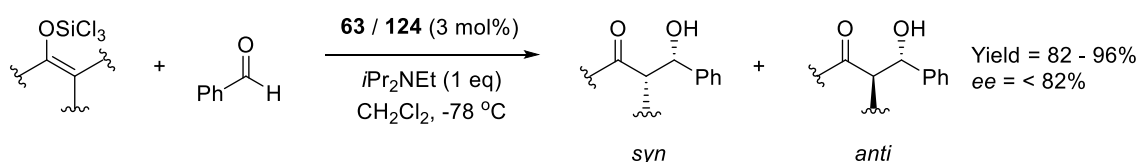
Scheme 55. Models proposed by A: Takenaka and B: Wheeler to explain the enantiofacial selectivity of helical *N*-oxide catalyst **122 within propargylation reactions.**^{138,141}

1.4.1.3 Aldol reactions

N-Oxide catalysed aldol reactions, employing trichlorosilyl enol ethers as enolate donors, are also believed to proceed *via* a mechanism analogous to that reported previously for the allylation of aldehydes (Scheme 56).^{92,93,144-147} Typically, the geometry of the enol ether determines the diastereoselectivity of the aldol product formed, with (*Z*)-silyl enol ethers generating *syn*-adducts and (*E*)-silyl enol ethers affording *anti*-adducts, which is consistent with aldol reactions proceeding *via* a 6-membered cyclic transition state (**123**) (Scheme 56).^{92,93,144-147} Specifically, the *N,N'*-dioxide catalyst (**63** or **124**, Figure 13) is believed to chelate to the silicon, generating a hexacoordinate octahedral environment about the silicon atom and a chair-like transition state.^{92,93,144-147} However, it was observed that the aldol reaction of (*E*)-cyclic enol ethers catalysed by bulky monodentate *N*-oxides **70** and **125** (Figure 13), unexpectedly generate *syn*-adducts.^{92,93,144} Therefore, it has been proposed that in some cases the reaction may alternatively proceed *via* boat-like transition state **126**, with the cationic silicon occupying a trigonal bipyramidal environment (Scheme 57); a phenomenon which has also been observed when using bulky monodentate phosphoramides.^{92,93,144,148}

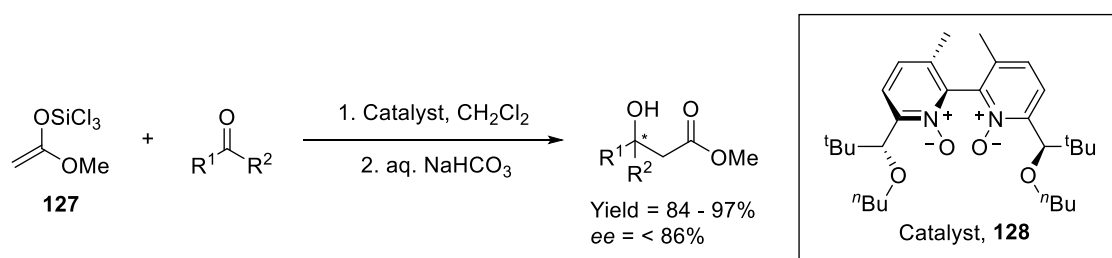
Scheme 56. Catalytic cycle for *N*-oxide promoted aldol reactions.¹⁴⁵Figure 13. *N*-Oxide catalysts developed by Nakajima for asymmetric aldol reactions.¹⁴³Scheme 57. Transition state models for the *N*-oxide promoted aldol reaction.^{93,144}

In 2004, Nakajima *et al.* determined that *N,N'*-dioxides **63** and **124** could catalyse the asymmetric addition of silyl enol ethers to aldehydes, with a maximum enantioselectivity of 82% *ee* achieved for aromatic aldehydes (Scheme 58).^{92,93,144} The use of achiral *N*-oxides, namely pyridine *N*-oxide, as Lewis base catalysts for racemic aldol reactions was reported by Hagiwara *et al.* shortly afterwards.¹⁴⁷ Moderate to good yields were achieved for both aromatic and aliphatic aldehydes, including those containing acid and base sensitive functional groups, such as pyridinecarboxaldehyde.¹⁴⁷



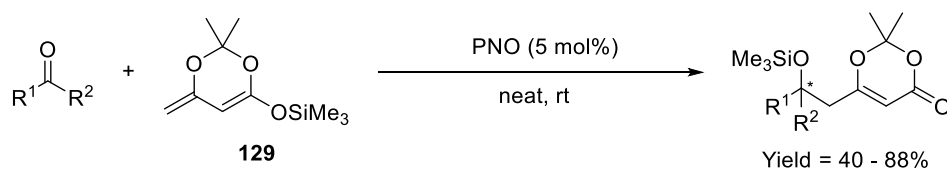
Scheme 58. Aldol reaction of benzaldehyde promoted by catalysts **63** or **124**.¹⁴⁴

Ketones represent a more problematic substrate class for the aldol reaction due to the endothermic nature of the reaction and their reduced enantiofacial discrimination, relative to aldehydes, arising from the increased similarity in the size and electronics of the R substituents adjacent to the carbonyl.^{93,145,146} In order to circumvent these issues highly reactive silyl ketene acetals (**127**) and chiral Lewis basic *N*-oxides have been employed (Scheme 59).^{93,145,146} Denmark and co-workers have reported that *N,N'*-dioxide **128** is a promising catalyst for this transformation, with enantioselectivities of up to 86% *ee* achieved.^{93,145,146} As previously seen, aromatic ketones afforded superior results (49-86% *ee*), whilst aliphatic and α,β -unsaturated substrates gave lower enantioselectivities (8-43% *ee*).^{93,145,146}

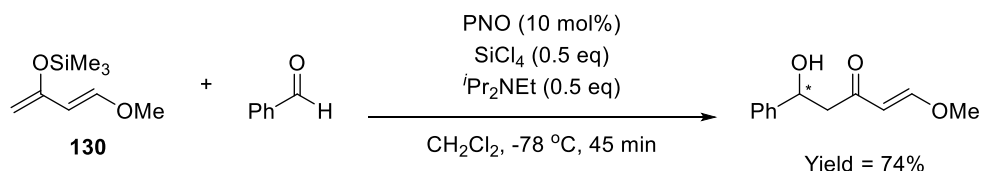


Scheme 59. Aldol reaction of ketones promoted by *N,N'*-dioxide **128**.^{145,146}

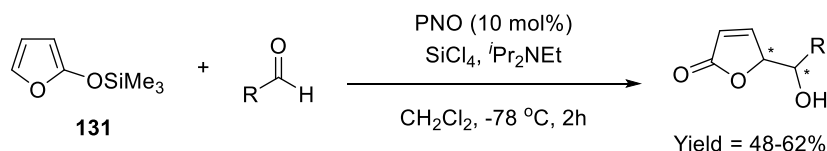
More recently, Scettri and co-workers reported that vinylogous aldol reactions between aldehydes/ketones and the more poorly nucleophilic dioxinone derived enol ether **129** were successfully catalysed by PNO, with the reactions run neat (Scheme 60).^{149,150} Similarly, the aldol reactions of Danishefsky's diene **130** (Scheme 61) and 2-(trimethylsiloxy)furan (TMSOF) **131** (Scheme 62) can be catalysed by PNO, with the latter transformation also proceeding with γ -addition of the TMSOF enolate species to the aldehyde.^{149,150}



Scheme 60. PNO catalysed vinylogous aldol reaction using dioxinone derived enol ether **129** as the nucleophile.¹⁵⁰



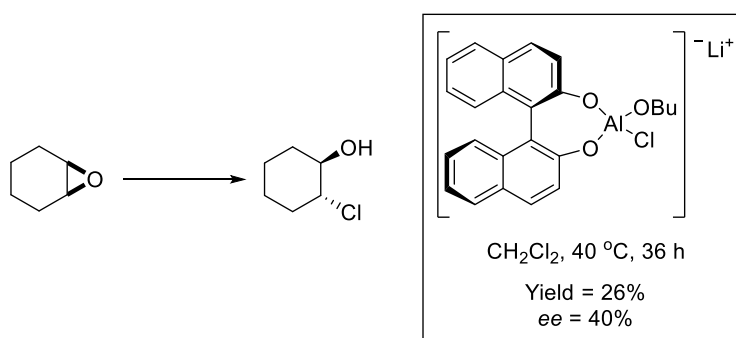
Scheme 61. PNO catalyzed vinylogous aldol reaction using Danishefsky's diene **130** as the nucleophile.¹⁴⁹



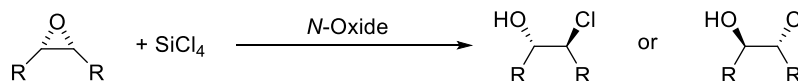
Scheme 62. PNO catalyzed vinylogous aldol reaction using TMSOF **131** as the nucleophile.¹⁴⁹

1.4.1.4 Enantioselective ring opening of *meso*-epoxides

The enantioselective ring opening of *meso*-epoxides using a chloride nucleophile allows access to vicinal halohydrins, which contain two contiguous stereocentres.^{93,151-154} Classically, this transformation was achieved using stoichiometric quantities of chiral Lewis acid halides, which incorporated both the activator and nucleophile (Scheme 63).^{152,155} However, more recently the concept of nucleophilic activation of Lewis acids (SiCl₄) by Lewis bases has been applied, with *N*-oxides commonly fulfilling the latter role (Scheme 64).^{152,153,155} The *N*-oxide catalysts developed for this purpose can be divided into four different categories based on their sense of chirality: planar, axial, central or helical.¹⁵³



Scheme 63. Ring opening of *meso*-epoxides with chiral Lewis acid halides.¹⁵⁵



Scheme 64. *N*-Oxide promoted ring opening of *meso*-epoxides with silicon tetrachloride.

In 2001, Fu *et al.* reported that the planar chiral *N*-oxide catalyst **132** had been successfully employed for the desymmetrisation of racemic epoxides, achieving enantioselectivities of up to 98% *ee* (Figure 14).^{153,154,156} The authors found that *meta*-substitution of the C₅Ar₅ ring of the catalyst was crucial for achieving high levels of stereochemical control, which has been attributed to the ability of this ligand to block the bottom face of the *N*-oxide effectively; therefore creating a superior chiral environment.^{153,156} Whilst electronic variations to aryl rings of the epoxide were well tolerated (91-98% *ee*), alkyl substituted epoxides were ring opened with only moderate enantioselectivities (50% *ee*).^{153,156}

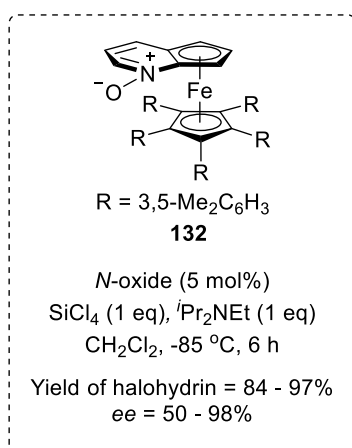


Figure 14. Planar chiral *N*-oxide catalyst (132) utilised for the desymmetrisation of racemic epoxides.¹⁵⁶

Catalyst **124**, which was initially investigated by Nakajima and co-workers for the enantioselective allylation of aldehydes, achieved excellent levels of stereochemical control for the ring opening of *cis*-stilbene oxide (Figure 15).^{94,151,153} It was documented that the chiral purity of the chlorohydrin was greatly influenced by the identity of the solvent, whilst alternative nucleophiles, such as methyl-, allyl- or phenyltrichlorosilane, afforded only the racemic product; albeit in good yields.^{151,154} Good enantioselectivities were also obtained for the small number of alkyl substituted variants examined (70-74% *ee*).^{151,153} However, the developed protocol could not be successfully extended to cyclic substrates, with a racemic halohydrin being obtained for cyclohexene oxide.^{151,153}

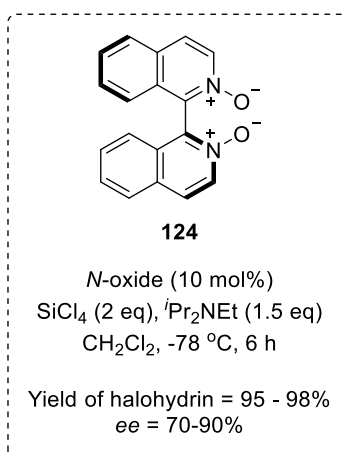


Figure 15. Axially chiral *N,N'*-dioxide catalyst (**124**) employed for the enantioselective ring opening of epoxides.¹⁵¹

Terpene-derived *N*-oxides **66** and **102** have also been applied to the enantioselective ring opening of epoxides (Figure 16).^{91,153,157} Interestingly, whilst *N,N'*-dioxide **102** was relatively effective at controlling the enantioselective ring opening of *cis*-stilbene oxide, *N*-oxide **66** was the first catalyst reported to provide cyclic halohydrins in high enantioselectivities, with the best results achieved for larger ring systems (>7 carbons).^{91,153,157} As previously observed for allylation reactions, an even numbered chelate ring results in higher levels of stereochemical control.^{91,153,157} Interestingly, subjection of tricyclic *exo*-norbornene oxide to the developed desymmetrisation conditions using catalyst **66** resulted primarily in the formation of **134** (56% yield, 90% *ee*) via a Wagner-Meerwein rearrangement, as opposed to the vicinal chlorohalohydrin (Scheme 65).¹⁵⁷ Based on the mechanism by which **134** is formed, the authors postulate that there must be substantial polarisation of the C-O bond upon coordination of the epoxide to the lewis acidic silicon; indicating that the ring opening step may not follow a strict S_N2 mechanism.¹⁵⁷ In this particular example, coordination facilitates bond cleavage and the formation of cationic intermediate **133**.¹⁵⁷

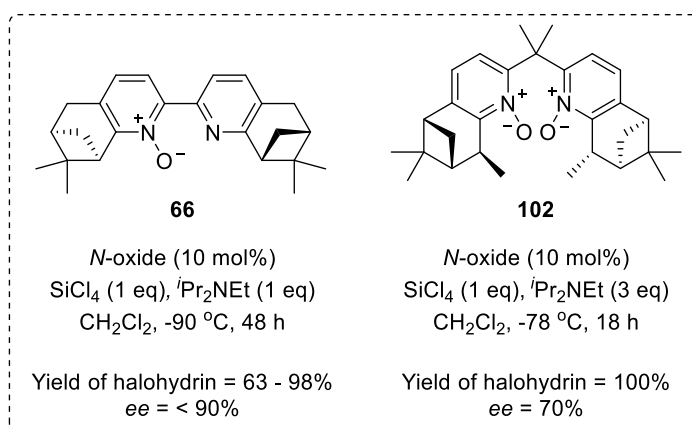
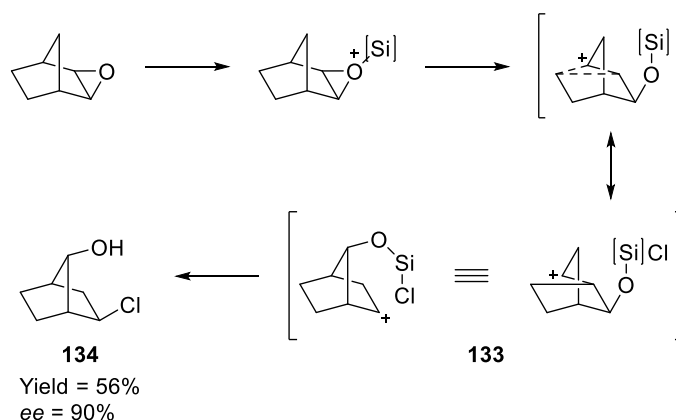


Figure 16. Optimised conditions for the enantioselective ring opening of epoxides with terpene-derived N-oxides **66** and **102**.^{91,153,157}



Scheme 65. Wagner-Meerwein rearrangement of *exo*-norbornene oxide observed upon treatment with SiCl₄ in the presence of N-oxide **66**.¹⁵⁷

More recently, Ramanathan *et al.* reported that bipyridine *N,N'*-dioxide **135**, which transiently provides an axially chiral environment upon chelation to silicon, affords aromatic halohydrins in high yields (92-97%) and enantioselectivities (78-93%) from the desymmetrisation of *cis*-stilbene oxide derivatives with SiCl₄ (Figure 17).¹³³ Limited success was achieved with cyclic *meso*-epoxides, with only moderate yields and enantiomeric excess reported (65-84% yield, 22-69% *ee*).¹³³ However, in accordance with previous findings, the largest ring (cyclooctene) provided the best of these results.¹³³ To date **136**, which is comprised of two substituted pyridine N-oxides fused to a bicycle[3.3.1]nonane backbone, is the most effective catalyst for the enantioselective ring opening of small cyclic epoxides (5-8 carbons, 59-85% yield, 47-88% *ee*).¹⁵⁸ Unusually, the smallest species afforded the product of the highest enantiopurity.¹⁵⁸ The diaryl substituted analogue **137** was found to successfully promote the enantioselective Wagner-Meerwein rearrangement of norbornene oxide, generating **134** in 50% yield and 96% *ee*.¹⁵⁸

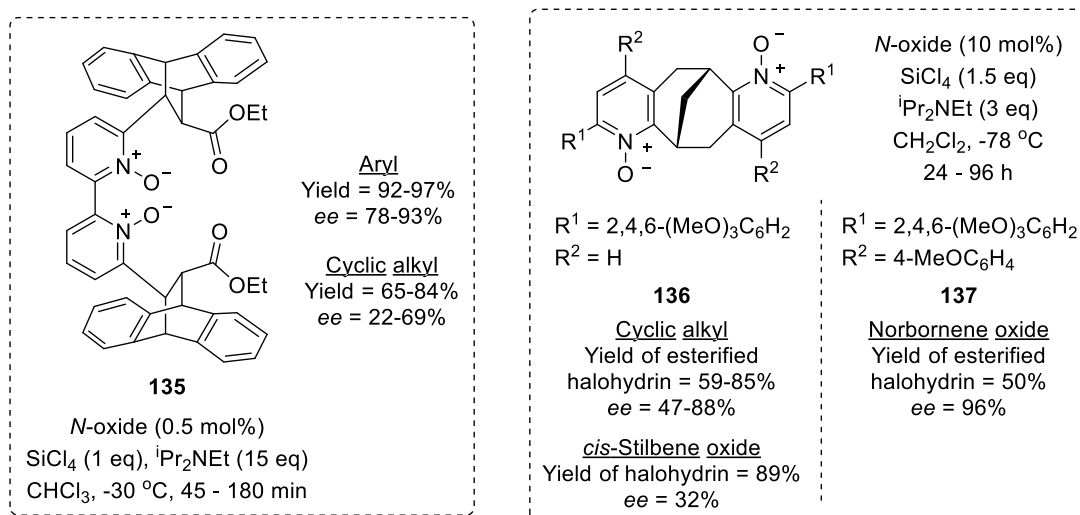


Figure 17. Optimised conditions for the enantioselective ring opening of epoxides with *N*-oxides 135-137.^{133,158}

N-Oxide **138**, which is a 1-aza[6]helicene derivative, exhibits helical chirality and has been reported to achieve excellent enantioselectivities for the desymmetrisation of aromatic based epoxides (Figure 18).^{153,159} As observed with several other *N*-oxides, the enantioselectivity achieved for epoxides functionalised with alkyl substituents was moderate, with cyclic substrates also resulting in halohydrins with low enantiomeric excess.^{153,159}

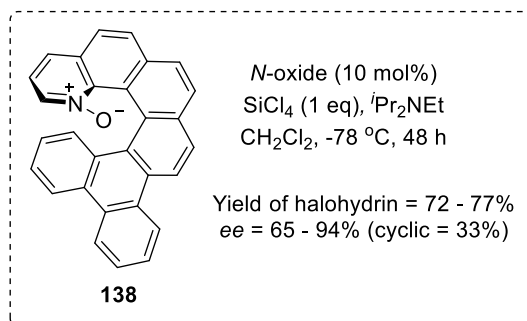
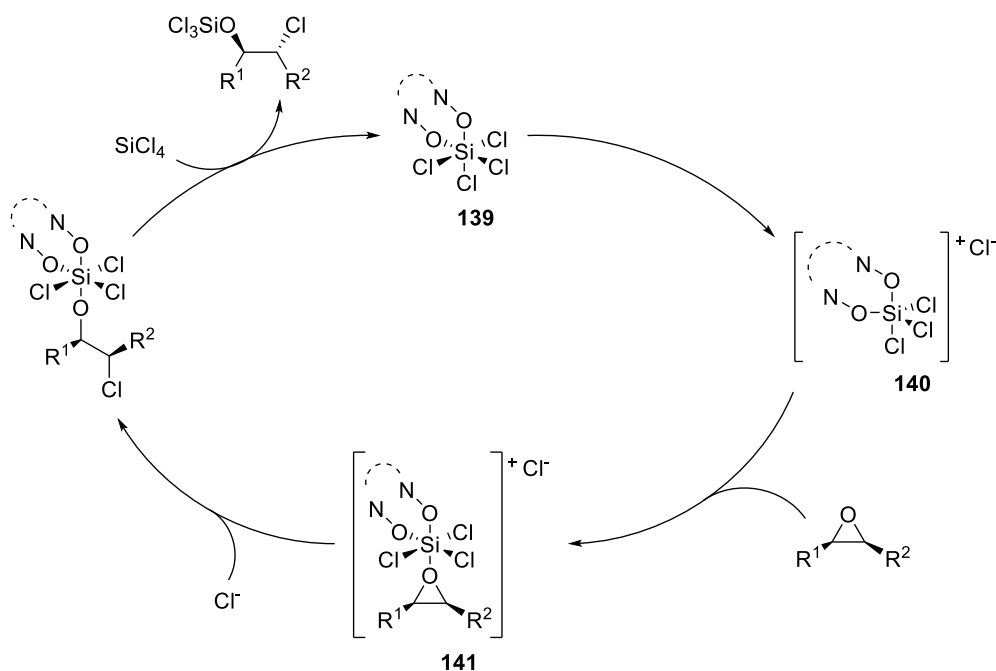


Figure 18. Conditions for the desymmetrisation of aromatic based epoxides with *N*-Oxide 138, which exhibits helical chirality.^{153,159}

In terms of the mechanism, it has been postulated that the *N*-oxide coordinates to the silicon to generate a hypervalent silicate species **139** with enhanced Lewis acidity, as determined from ¹H and ²⁹Si NMR studies (Scheme 66).^{93,152,153,155-157} Additionally, it has been suggested that the *N*-oxide catalyst primarily exists in solution as part of this complex as opposed to a discrete unbound entity, due to the reaction being zero order in SiCl₄.^{92,152,153,155,156} The *meso*-epoxide can then coordinate to the cationic silicate species **140** forming **141** and as a result is activated towards ring opening by the chloride ion, which is thought to proceed *via* an S_N2 type mechanism.^{92,93,152,153,155-157}

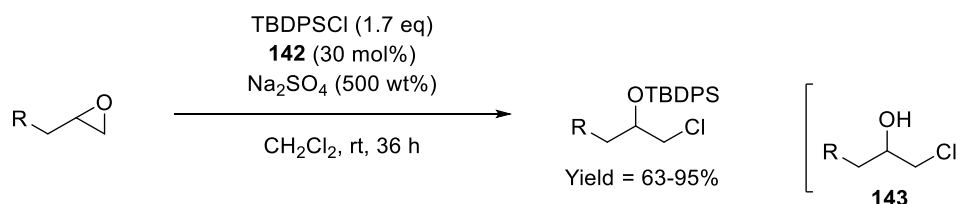


Scheme 66. Proposed mechanism for *N*-oxide promoted ring opening of *meso*-epoxides.¹⁵²

The group of Fu established that the enantiomeric excess of the *N*-oxide catalyst is correlated in a positive but non-linear manner with the enantiometric excess achieved for the derived chlorohydrin product; an observation for which two rationales have been proposed.^{151-153,155,157} Nakajima *et al.* attributed this phenomenon to the participation of two molecules of the Lewis basic catalyst in the rate and stereochemistry determining step.^{151-153,155,157} Additionally, as bidentate *N*-oxides often induce higher enantiomeric excesses relative to their corresponding mono *N*-oxides, it has been suggested that a hexacoordinate silicon species is formed.^{151-153,155,157} Alternatively, it has been postulated that the second molecule of the Lewis base may coordinate within a silicate counter anion.^{151,155,157} It is believed that the role of the diisopropylethylamine within these reactions is to scavenge evolved HCl, which can act as a competing chlorine source to promote an undesired, non-stereoselective ring opening of the epoxide.^{151,153}

In the racemic variant, structurally simple electron rich 4-methoxypyridine *N*-oxide (**142**) has been reported to catalyse the regioselective chlorosilylation of epoxides with bulky silylating reagents, namely *tert*-butyldiphenylsilyl chloride (TBDPSCI) and triphenylsilyl chloride (Scheme 67).¹⁶⁰ Installation of these more bulky silyl species, which was not possible using previously reported methods, aids with retention of the protecting group during subsequent transformations.¹⁶⁰ Deprotection of the products by *in situ* generated acid was minimised by the addition of sodium sulfate and a series of TBDPS silylated halohydrins were isolated in good to excellent yields (63-95%) and regioselectivities.¹⁶⁰ With the exception of styrene oxide, for which a stable benzylic carbocation can be generated, the chloride reacted at the least sterically

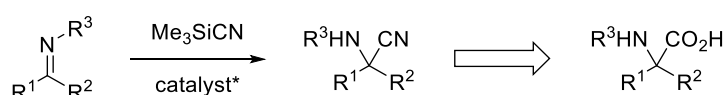
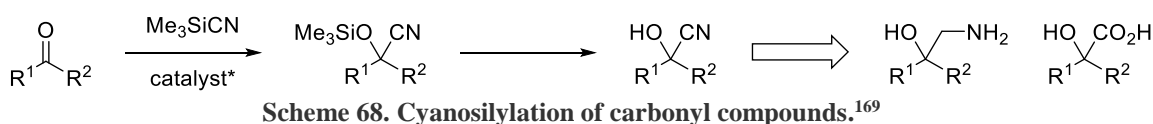
encumbered epoxide carbon.¹⁶⁰ It was determined that silylation occurs in concert with ring opening, as no reaction was observed upon subjecting alcohol **143** (R = OPh) to the reaction conditions.¹⁶⁰



Scheme 67. 4-Methoxypyridine *N*-oxide (**142**) catalysed ring opening of epoxides to form TBDPS protected halohydrins.¹⁶⁰

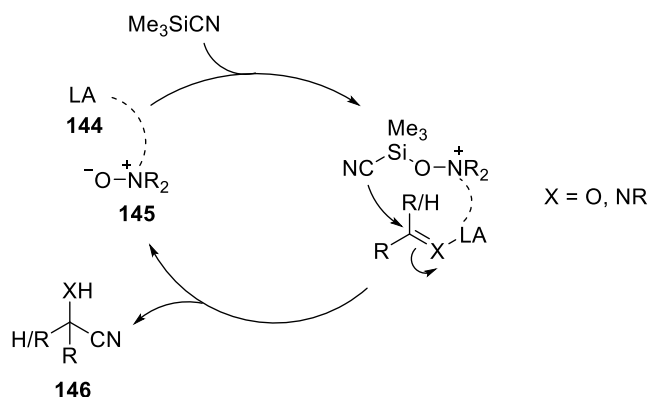
1.4.1.5 Cyanosilylation of carbonyl compounds and imines

Enantioenriched cyanohydrins, which are precursors to a range of versatile building blocks such as α -hydroxy acids and β -aminoalcohols, can be prepared from the asymmetric cyanosilylation of aldehydes and ketones (Scheme 68).^{93,161-165} Similarly, α -amino nitriles, which are generated from the asymmetric cyanosilylation of imines (enantioselective Strecker reaction), provide access to chiral α -amino acids (Scheme 69).¹⁶⁶ Within these reactions, trimethylsilyl cyanide (TMSCN) is generally employed as a safer and more reactive source of cyanide than HCN or KCN.^{167,168}



N-Oxides have been explored as Lewis basic catalysts for the reaction of silicon bound cyanide nucleophiles with carbonyl compounds and imines. However, the asymmetric variants of these reactions are almost exclusively conducted in the presence of a Lewis acidic co-catalyst; typically in the form of a transition metal complex.¹⁷¹ The Lewis acidic and Lewis basic components can be tethered together in one molecule, as a bifunctional activation catalyst, or alternatively they can be utilised as discrete entities, which is described as a catalytic double-activation method.^{169,172} For both methods, it has been determined that these two components act synergistically, with the Lewis acid part activating the carbonyl or imine functionality of the reactant and the Lewis basic *N*-oxide component increasing the reactivity of the silicon bound

cyano nucleophile by coordinating to the TMS-CN to generate a hypervalent silyl species (Scheme 70).^{169,170,173,174} Several groups have conducted both ^1H and ^{29}Si NMR spectroscopic studies to establish that an interaction exists between the *N*-oxide and silyl group of TMS-CN.^{170,172-175}

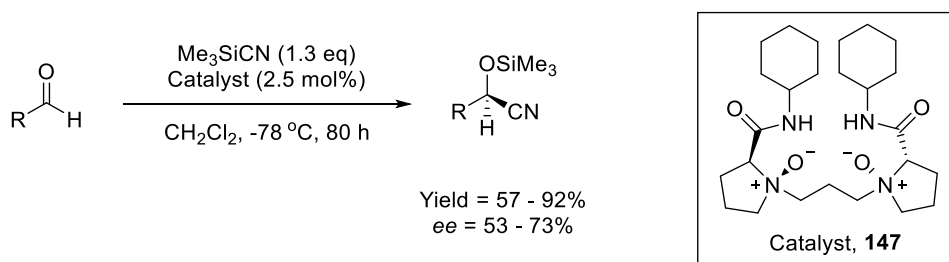


Scheme 70. Generic mechanism of cyanosilylation reactions.^{173,176,177}

Upon coordination, the cyano group attacks the carbonyl/imine, which exhibits prochirality in the asymmetric variant, to afford the desired product **146** and regenerate catalysts **144** and **145** (Scheme 70).^{161,173,175-177} Several *N*-oxides have been designed to fulfil the dual role of controlling reactivity and enantioselectivity within cyanation reactions, however in other cases the metal-ligand complex imparts chirality to the product and the *N*-oxide acts solely as a rate accelerant.¹⁶⁹

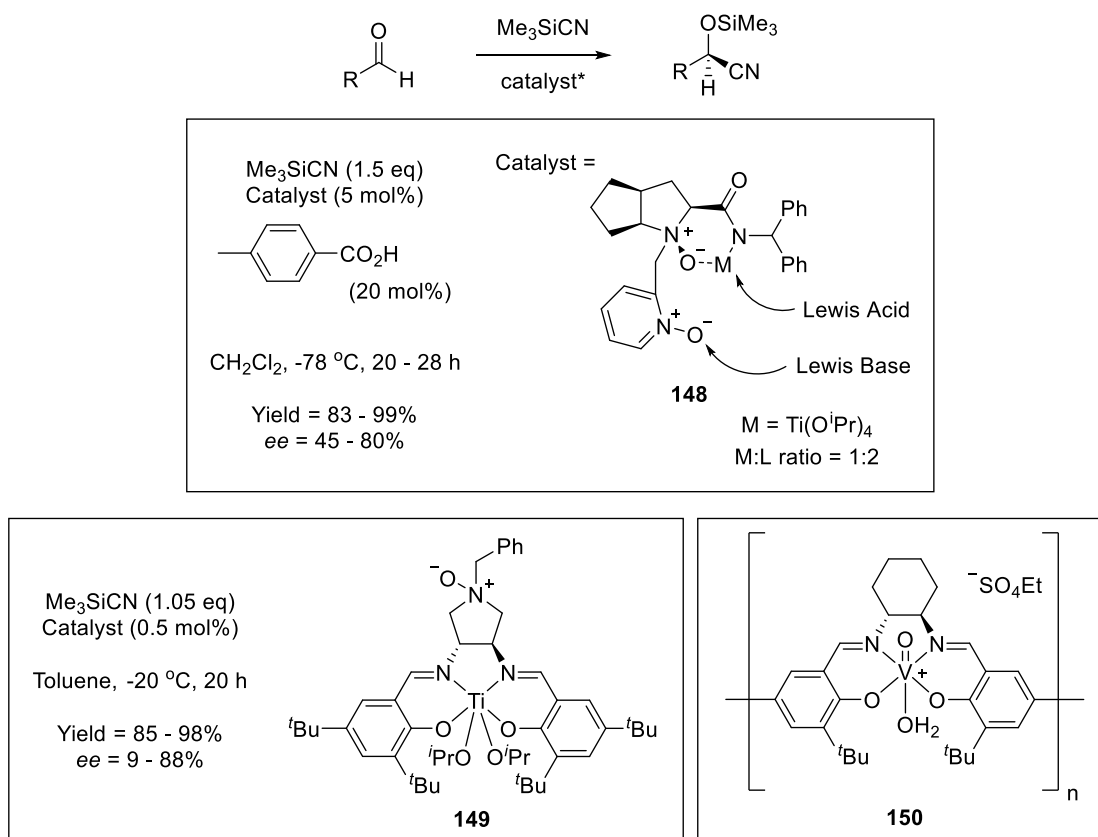
1.4.1.5.1 Cyanosilylation of aldehydes

In 2004, Kim *et al.* reported that commercially available NMO could successfully catalyse the cyanosilylation of aldehydes to afford racemic trimethylsilyl ethers.¹⁷⁸ Typically, these reactions were complete within 20 minutes for both aromatic and aliphatic substrates and high yields of the *O*-silyl cyanohydrin were isolated (90-97%).¹⁷⁸ Since this initial report, several examples of asymmetric silylcyanations of aldehydes (co)catalysed by *N*-oxides have emerged in the literature. Feng and co-workers developed the proline derived *N,N'*-dioxide **147** for this purpose (Scheme 71).¹⁷⁹ Enantioselectivities of up to 73% *ee* were achieved with loadings as low as 2.5 mol%, although extended reaction times of 80 hours were required.¹⁷⁹ However, *N,N'*-dioxide **147** still remains the only example of a chiral *N*-oxide having independently been used to catalyse the asymmetric cyanosilylation of aldehydes.¹⁷⁹

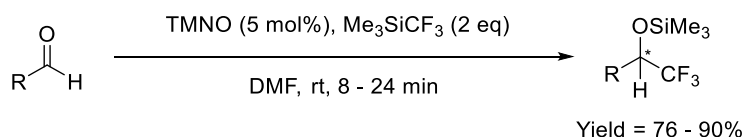


Scheme 71. Cyanosilylation of aldehydes promoted by *N,N'*-dioxide **147**.¹⁷⁹

The same group have also reported that the *N,N'*-dioxide-Ti(O^{*i*}Pr)₄ bifunctional catalyst **148** can promote the cyanosilylation reactions in substantially shorter reaction times and slightly improved enantioselectivities (Scheme 72).¹⁸⁰ A modified bifunctional *N*-oxide salen Ti(IV) catalyst (**149**) has been developed by Sun and co-workers, which exhibits moderate to high levels of enantioselectivity and similar reaction times to that of **148**.¹⁷¹ Of particular interest for this catalyst is the relatively low loading (0.5 mol%) and the much reduced excess of TMSCN required (1.05 equiv. vs 1.5 equiv.) for the cyanosilylation reaction.¹⁷¹ Additionally, Khan *et al.* have demonstrated that the cyanosilylation of aldehydes can be catalysed by chiral, polymeric vanadium-salen complex **150**, which is typically employed in conjunction with 4-phenylpyridine *N*-oxide as a rate-enhancing additive (Scheme 72).¹⁷⁶ However, in contrast to the other systems discussed, this complex can promote the asymmetric cyanosilylation reaction in the absence of the *N*-oxide, albeit with slightly longer reaction times (18 h vs 12 h).¹⁷⁶

Scheme 72. Catalysts developed for the cyanosilylation of aldehydes.^{171,176,180}

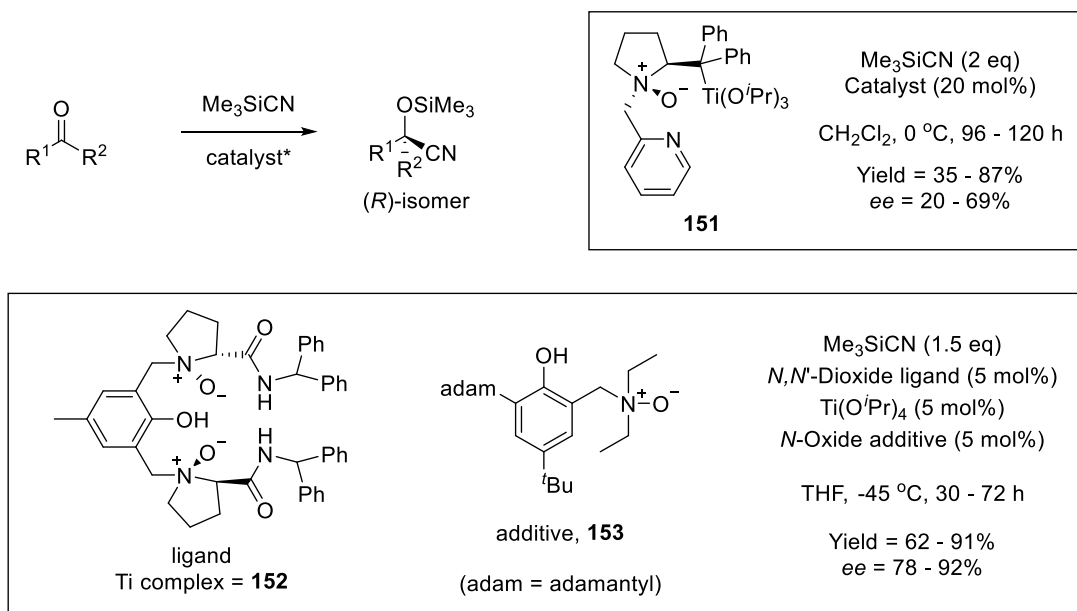
Interestingly, Prakash and co-workers have demonstrated that this methodology can be extended to the trifluoromethylation of aldehydes by substituting TMSCN for trifluoromethyltrimethylsilane (TMSCF_3) (Scheme 73).^{181,182} Specifically, trimethylamine *N*-oxide was employed as the organocatalyst, with good to high isolated yields of the desired adduct achieved.^{181,182} However, the use of DMF as the solvent was imperative for achieving high reaction rates and an acceptable catalyst loading.^{181,182}

Scheme 73. TMNO promoted trifluoromethylation of aldehydes.¹⁸²

1.4.1.5.2 Cyanosilylation of ketones

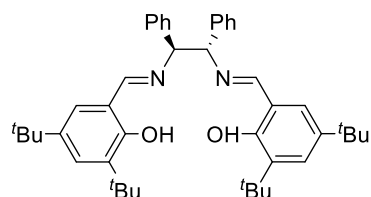
Feng and co-workers have played a prominent role in designing novel *N*-oxide based catalysts that are effective at promoting the asymmetric cyanosilylation of ketones.^{162,165,177,183,184} Initially, they investigated the use of chiral *N*-oxide- $\text{Ti}(\text{O}^i\text{Pr})_4$ complexes **151** and **152** as bifunctional activation catalysts (Scheme 74).^{162,165,177,183,184} While **151** gave the desired cyanohydrins with poor to moderate enantiomeric excess, *N,N'*-dioxide **152** induced much higher levels of

stereochemical control and improved substrate generality.^{162,165,177,183,184} Although *N,N'*-dioxide **152** could be employed with a reduced catalyst loading of 5 mol% and a lower excess of TMS-CN (1.5 equiv.) was required, the reaction needed to be performed in the presence of phenolic *N*-oxide **153** as an additive (5 mol%).¹⁶⁵ In all cases, the reaction times remained relatively high.^{162,165,177,183,184}

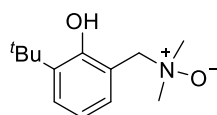


Scheme 74. *N*-Oxide based bifunctional catalysts developed for the stereoselective cyanosilylation of ketones.^{165,184}

Double-activation catalyst systems, which employ an achiral *N*-oxide and a chiral metal-based Lewis acid, were then explored.¹⁶⁹ Chiral titanium-salen complex **154** was employed in conjunction with *N*-oxides **155** and **156** and these systems were found to induce moderate to good levels of enantioselectivity for cyanohydrin formation (Scheme 75).^{163,172,185-187} The first of these catalyst systems employed higher loadings of the titanium-salen complex (10 mol% vs 2 mol%); typically allowing for slightly shorter reaction times (96 vs 120 h) and higher isolated yields.^{163,172,185-187} To date, the most successful catalyst system comprises of the chiral salen-aluminium complex **157** and achiral *N*-oxide **156** in a 2 : 1 molar ratio (Scheme 76).^{161,173} Feng and co-workers have found that under the optimised conditions good to excellent enantioselectivities can be achieved for the cyanosilylation of numerous aromatic and aliphatic ketones.^{161,173} This double-activation catalyst is remarkable in terms of its high catalytic turnover (aromatic ketones: ~200, aliphatic ketones: ~1000) as well as the low catalyst loadings required (0.5 mol% Al-complex **157**, 0.25 mol% *N*-oxide **156**).^{161,173} The reaction times have also been successfully reduced.^{161,173}



ligand
Ti complex = **154**

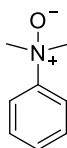


additive, **155**

Me₃SiCN (2 eq)
Ligand (10 mol%)
Ti(OⁱPr)₄ (10 mol%)
N-oxide additive (1 mol%)

CH₂Cl₂, -20 °C, 96 h

Yield = 68 - 96%
ee = 52 - 82%



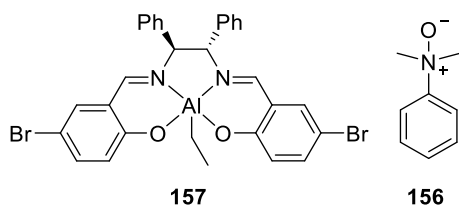
additive, **156**

Me₃SiCN
Ligand (2 mol%)
Ti(OⁱPr)₄ (2 mol%)
N-oxide additive (1 mol%)

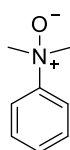
CH₂Cl₂, -20 °C, 120 h

Yield = 57 - 93%
ee = 64 - 84%

Scheme 75. Ti complex and *N*-oxide dual catalyst for enantioselective cyanosilylation of ketones.^{185,186}



157



156

For aromatic ketones:

Me₃SiCN (2 eq)
Al complex (0.5 mol%)
N-oxide additive (0.25 mol%)

THF, -20 °C, 24 - 72 h

Yield = 92 - 99%
ee = 79 - 93%

For aliphatic ketones:

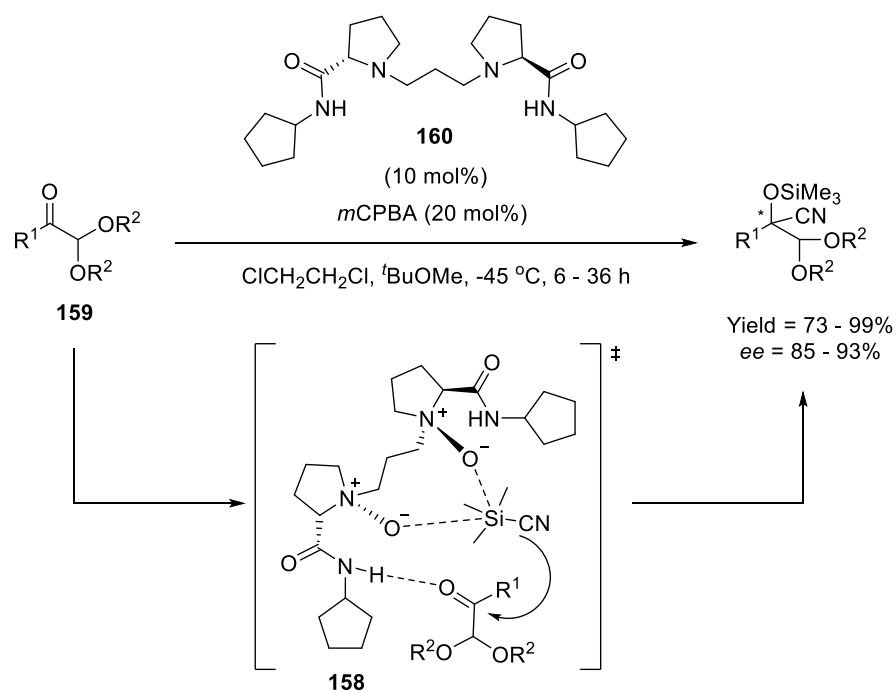
Me₃SiCN (2 eq)
Al complex (0.1 mol%)
N-oxide additive (0.05 mol%)

THF, -20 °C, 36 h

Yield = 80 - 99%
ee = 79 - 90%

Scheme 76. Al complex and *N*-oxide dual catalyst for enantioselective cyanosilylation of ketones.¹⁶¹

More recently, *N,N'*-dioxide **158**, which possesses C₂-symmetry, has been reported as an efficient catalyst for the enantioselective cyanosilylation of α,α -dialkoxy ketones **159** (Scheme 77).¹⁷⁵ Uniquely, this is a metal free transformation with *N,N'*-dioxide **158** synthesized *in situ* from the oxidation of the parent amine **160** with *m*CPBA.¹⁷⁵ It has been postulated that **158** is a bifunctional catalyst, with the *N*-oxide functionality assuming the role of the Lewis base and the NH of the amide portion participating as a hydrogen bond donor to enhance the electrophilicity of the substrate's carbonyl; collectively promoting nucleophilic addition.¹⁷⁵ Particularly high enantioselectivities and isolated yields of the desired cyanohydrin trimethylsilyl ethers have been achieved, with **158** exhibiting a high tolerance for both steric and electronic variations within the acetal ketone.¹⁷⁵



Scheme 77. Metal-free asymmetric cyanosilylation of α,α -dialkoxy ketones.¹⁷⁵

The groups of Feng and Kim have shown that NMO¹⁶⁹ and *N*-oxide **161**¹⁸⁸ are independently able to catalyse the achiral addition of TMSCN to ketones in excellent yields (91-99% and 78-99% respectively) (Figure 19).^{169,188} Additionally, quaternary ammonium salts have proved effective as alternative Lewis acids for the racemic variant of the cyanosilylation reaction, with these systems having the added benefit of not being air and moisture sensitive.^{167,169,188}

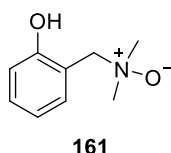
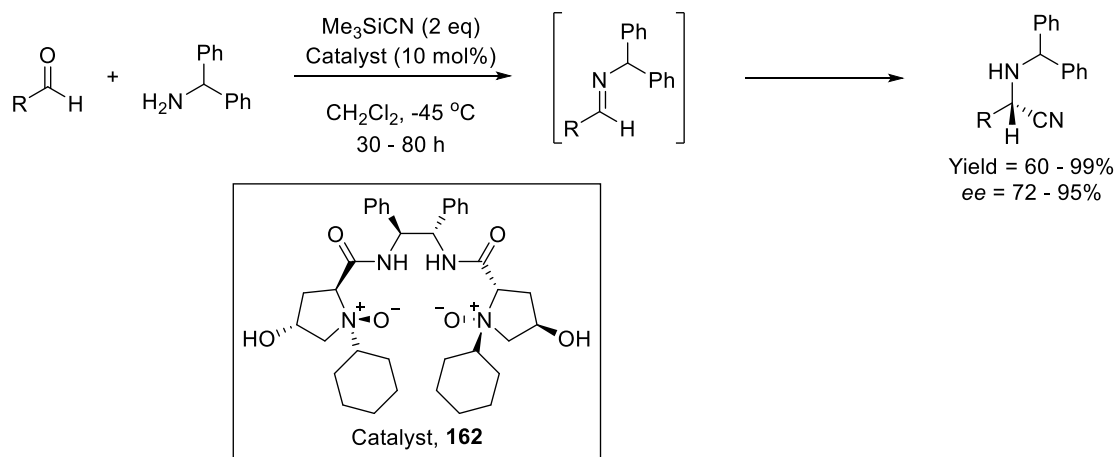


Figure 19. *N*-Oxide catalyst **161**.¹⁸⁸

1.4.1.5.3 Cyanosilylation of imines

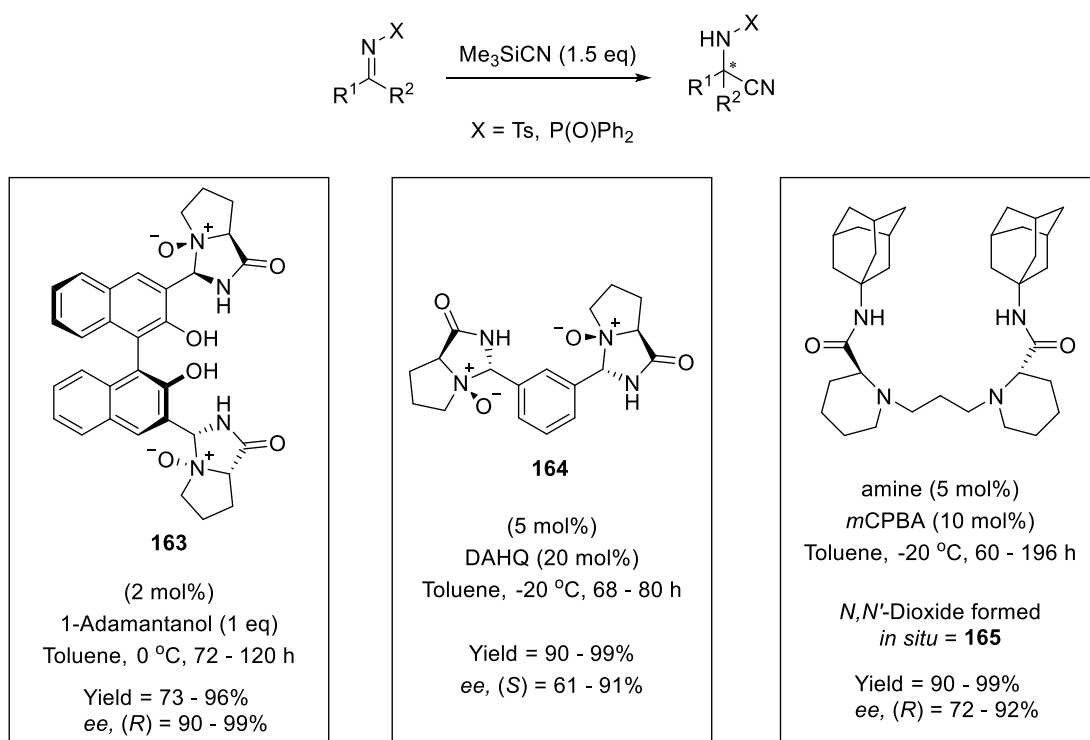
In the first examples of *N*-oxide promoted asymmetric Strecker reactions the *N*-oxide was shown to be functioning as a stoichiometric reagent rather than an organocatalyst.^{166,170} However, in 2008 Feng and co-workers demonstrated that *N,N'*-dioxide **162** could effectively catalyse the asymmetric cyanosilylation of aldimines when employed in substoichiometric quantities (10 mol%) (Scheme 78).¹⁸⁹ As described for catalyst **158**, *N,N'*-dioxide **162** operates as a bifunctional catalyst, as the amide moiety is able to enhance the electrophilicity of the imine through hydrogen bonding interactions.¹⁸⁹ The authors observed that superior reactivity and enantioselectivities were achieved when the imine was generated *in situ* from the corresponding aldehyde and amine, which they proposed could be attributed to the presence of water formed during the imine

condensation reaction.¹⁸⁹ Typically, high to excellent enantioselectivities were afforded and the methodology tolerated a wide substrate scope.¹⁸⁹ Interestingly, electron rich aromatic aldehydes represented the most reactive substrates, whilst electron deficient aldehydes exhibited enhanced enantioselectivities.¹⁸⁹



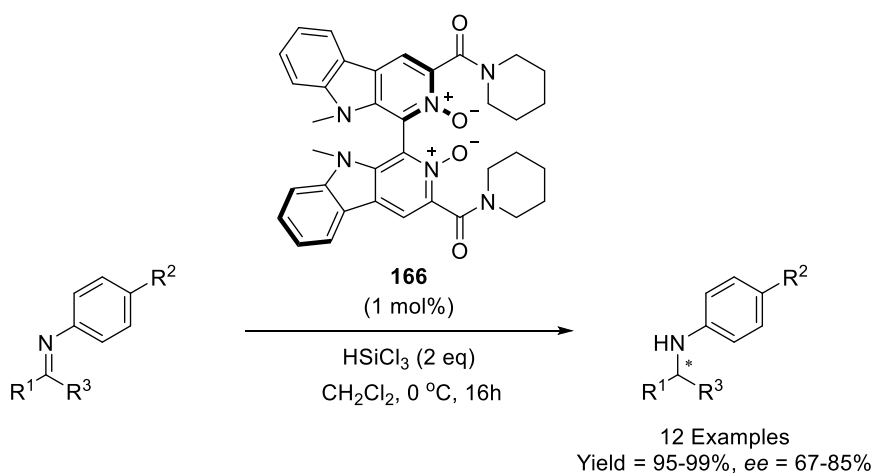
Scheme 78. Metal-free asymmetric cyanosilylation of *in situ* generated imines.¹⁸⁹

Chiral *N,N'*-dioxides **163** – **165** have been developed for the enantioselective cyanosilylation of *N*-tosyl and *N*-phosphoro ketoimines (Scheme 79).^{174,190,191} Of these catalysts, axially chiral *N,N'*-dioxide **163** induced the highest levels of enantioselectivity, however, the reaction needed to be performed in the presence of one equivalent of the additive adamantanol.^{174,191} It is interesting to note that **164** and **165** are bifunctional catalysts and **165** can be synthesized *in situ* from the corresponding amine.^{174,190}

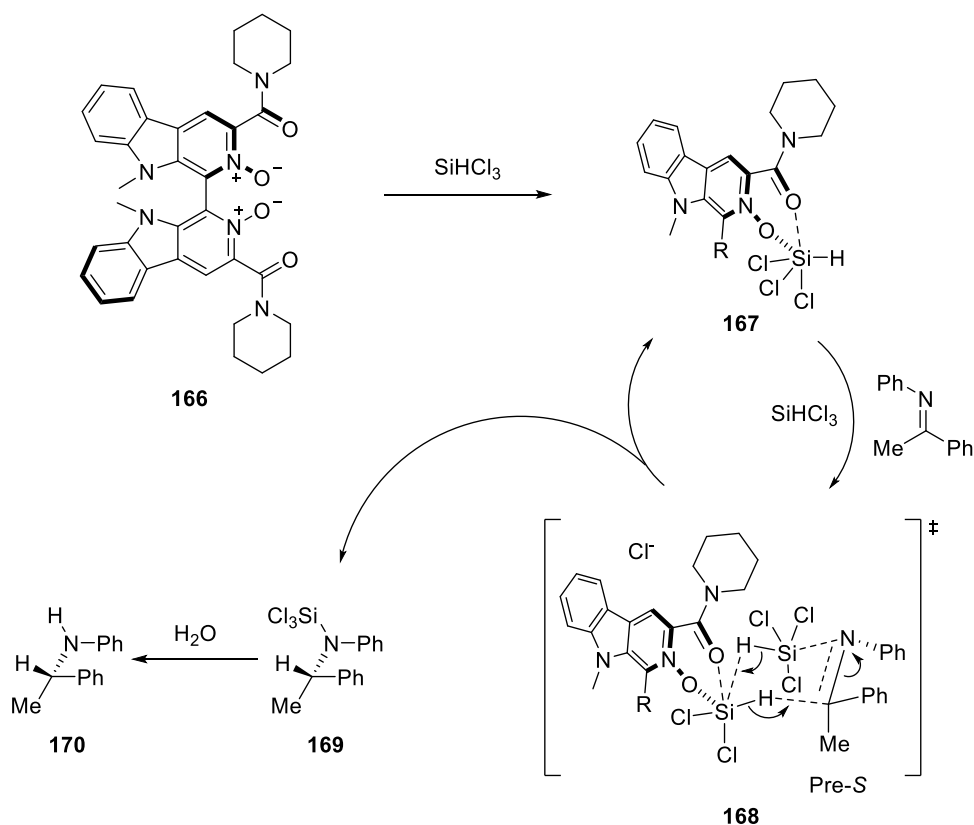


Scheme 79. Metal-free asymmetric cyanosilylation of imines promoted by *N,N'*-dioxides.^{174,190,191}

Chiral biscarboline *N,N'*-dioxide derivative **166** was successfully utilised by Zhu and co-workers within the trichlorosilane mediated enantioselective reduction of *N*-aryl ketoimines (Scheme 80).¹⁹² As reported for the allylation of aldehydes, subtle changes to the structure of the catalyst were found to influence the enantioselectivities achieved, with cyclic amides providing the greatest enantiocontrol.¹⁹² Accordingly, a library of chiral aryl amines were prepared in excellent yields (95-99%) and moderate to good stereoselectivities (67-85% *ee*); the highest of which were achieved for electron rich substrates.¹⁹² As detailed previously, the two *N*-oxide oxygens are positioned *trans* to one another, which results in the simultaneous but independent activation of two discrete silicon centres.¹⁹² Mechanistically, it is proposed that for each half of the catalyst one equivalent of SiHCl₃ is chelated to both the *N*-oxide and amide carbonyl to form species **167**, which enhances the nucleophilicity of the silicon bound hydride species (Scheme 81).¹⁹² This hydride then reacts with the imine, which is itself activated by a second equivalent of SiHCl₃, *via* the 6-membered cyclic transition state **168**.¹⁹² Hydrolysis of the resultant silylated species **169** then affords the desired reduction product **170**.¹⁹²



Scheme 80. Enantioselective reduction of *N*-aryl ketimines with trichlorosilane promoted by biscarboline *N,N'*-dioxide **166**.¹⁹²

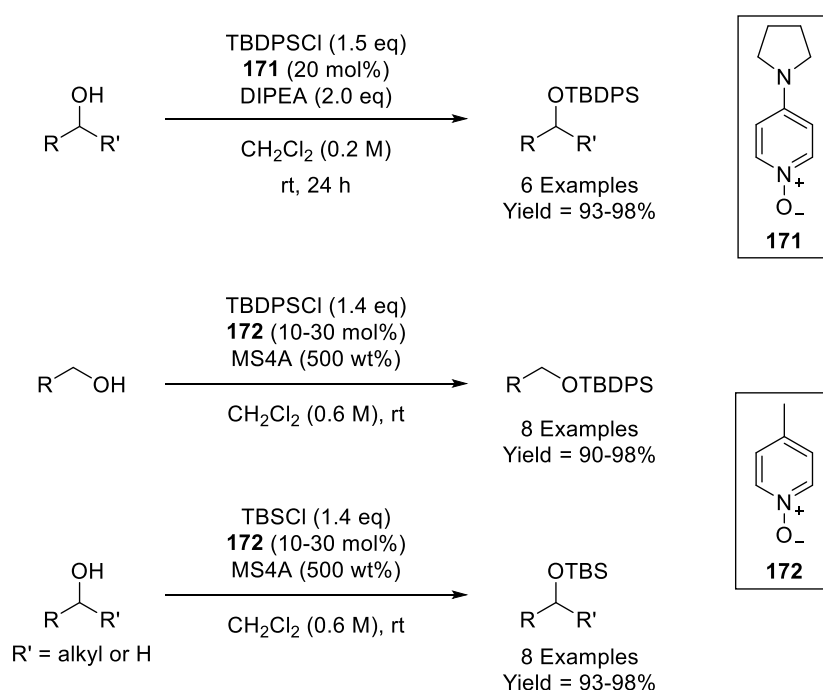


Scheme 81. Proposed mechanism for the enantioselective reduction of *N*-aryl ketimines with trichlorosilane catalysed by biscarboline *N,N'*-dioxide **166**.¹⁹²

1.4.1.6 Silylation of alcohols

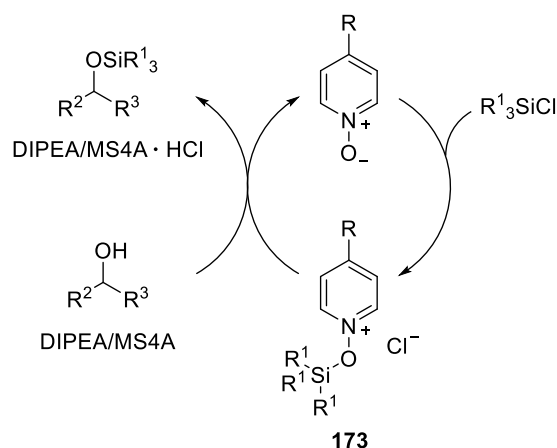
Yoshida and Takao have reported that electron rich pyridine *N*-oxide derivatives can catalyse the direct silylation of alcohols under mild conditions; providing the target silyl ethers in excellent yields (90-98%) (Scheme 82).^{193,194} 4-Pyrrolidinopyridine *N*-oxide (PPYO, **171**) was found to be

a superior catalyst for installing the *tert*-butyldiphenylsilyl (TBDPS) ether protecting group onto secondary alcohols, which is often challenging due to the steric encumbrance involved.¹⁹³ This methodology was amenable to cyclic and acyclic systems as well as a hindered *ortho*-disubstituted phenol.¹⁹³ In an extension of this work, the authors determined that 4-methylpyridine *N*-oxide (**172**) is effective for promoting the chemoselective protection of primary alcohols in the presence of secondary alcohols and phenols.¹⁹⁴ Although the TBDPS etherification of secondary alcohols was not achieved, *tert*-butyldimethylsilyl (TBS) ethers derived from cyclic secondary alcohols were afforded in excellent yields.¹⁹⁴ Whilst the initial system employed diisopropylethylamine to scavenge the evolved HCl, it was found that this basic additive could be substituted for molecular sieves (MS4A) in combination with 4-methylpyridine *N*-oxide.^{193,194}



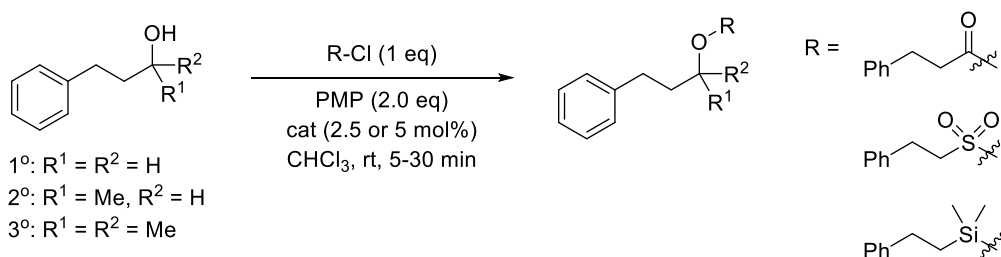
Scheme 82. *N*-Oxide catalysed silylation of alcohols.^{193,194}

In accordance with other silicon mediated reactions, the aromatic *N*-oxide is proposed to coordinate to the silylating reagent to form silicate complex **173** (Scheme 83).^{193,194} An interaction between such Lewis acidic and Lewis basic components was confirmed by ¹H NMR spectroscopic studies.^{193,194} Nucleophilic attack of the activated complex by the alcohol then generates the desired silyl ether and regenerates the *N*-oxide catalyst.^{193,194}

Scheme 83. Mechanism for the *N*-oxide catalysed silylation of alcohols.^{193,194}

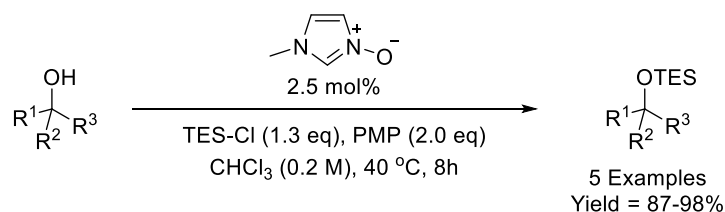
1.4.2 Protection of alcohols

Also in the context of alcohol protection, *N*-oxides have been successfully employed as catalysts for the acylation, sulfonylation and phosphorylation of hydroxyl functionalities. For instance, Spivey and co-workers reported that aromatic *N*-oxides are promising catalysts for the acylation, sulfonylation and silylation of hydroxyl groups, which involves treatment of an alcohol with either an acyl chloride, sulfonyl chloride or silyl chloride as required (Table 1).¹⁹⁵ Whilst DMAPO was found to promote the acylation of both primary and secondary alcohols, the parent amine (DMAP) was found to exhibit a higher catalytic activity (Table 1, entries 1-3).¹⁹⁵ Alternatively, 1-methylimidazole *N*-oxide (NMI-O) among other *N*-oxides was typically reported to be one of the most effective Lewis basic catalysts for the synthesis of sulfonate esters and silyl ethers from both primary and secondary alcohols (Table 1, entries 4-7).¹⁹⁵

Table 1. Aromatic *N*-oxides as catalysts for the acylation, sulfonylation and silylation of alcohols.¹⁹⁵

Entry	Reaction	Catalyst	1° Yield (%)	2° Yield (%)	3° Yield (%)
1	Acylation	-	51	10	0
2	Acylation	DMAP	92	27	0
3	Acylation	DMAPO	67	29	0
4	Sulfonylation	-	61	56	0
5	Sulfonylation	NMI-O	97	93	0
6	Silylation	-	53	32	0
7	Silylation	NMI-O	>99	>99	72

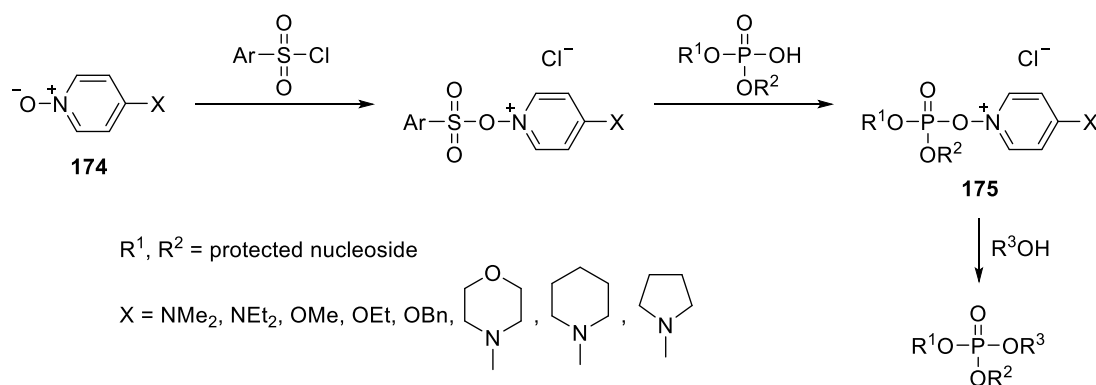
Significantly, this catalytic system was effective at installing a silyl group onto a tertiary alcohol (Table 1, entry 7) and was subsequently applied to the synthesis of a range of sterically encumbered triethylsilyl (TES) ethers (Scheme 84).¹⁹⁵ Such bulky ethers are more stable under acidic/basic conditions and were isolated in excellent yields (87-98%), with this methodology representing the first example of an *N*-oxide catalysed procedure for the silylation of *tert*-alcohols where TMSCl may be substituted for a larger silylating reagent.¹⁹⁵



Scheme 84. NMI-O catalysed silylation of tertiary alcohols with TES-Cl.¹⁹⁵

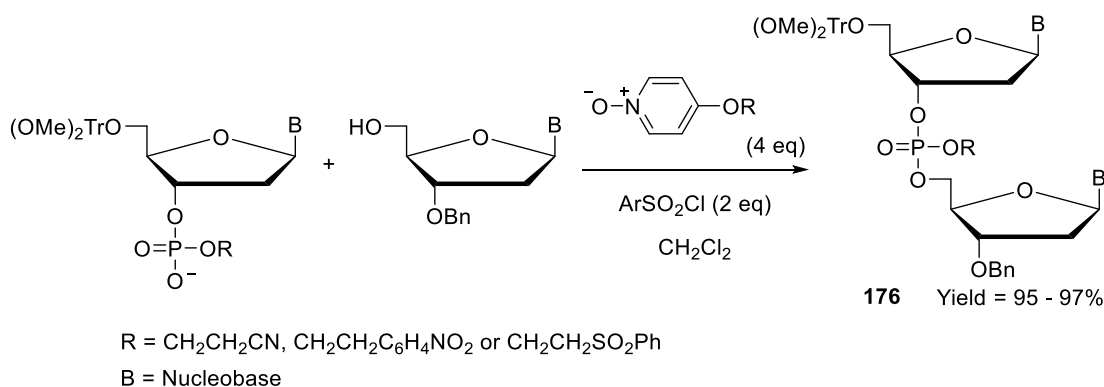
1.4.3 Organophosphorus chemistry

The use of *N*-oxides as organocatalysts is not restricted to silicon chemistry, with applications in organophosphorus chemistry dating back to 1985.¹⁹⁶⁻¹⁹⁸ For instance, 4-substituted pyridine *N*-oxides **174** have been extensively investigated by Efimov and co-workers as nucleophilic catalysts for phosphotriester bond formation, which has important implications for nucleotide and ultimately DNA synthesis (Scheme 85).¹⁹⁶⁻¹⁹⁸ In order to elucidate information on the reaction mechanism, the authors conducted a series of ¹H and ³¹P NMR spectroscopy studies of phosphorylation reactions, which were found to be consistent with the formation of activated, phosphate intermediate **175** as shown in Scheme 85.¹⁹⁶⁻¹⁹⁸ ¹H NMR spectroscopic studies revealed a downfield shift of the α - and β -protons of the pyridine ring in the intermediate relative to 4-dimethylaminopyridine *N*-oxide (DMAPO), suggesting reduced electron density on the nitrogen.¹⁹⁶⁻¹⁹⁸ Additionally, ³¹P NMR spectroscopic analysis demonstrated the appearance of a doublet at 12 ppm, with a coupling constant of 4 Hz, which is indicative of ¹⁵N – ³¹P spin – spin coupling.¹⁹⁶⁻¹⁹⁸



Scheme 85. *N*-Oxides as nucleophilic catalysts for phosphotriester bond formation.¹⁹⁶

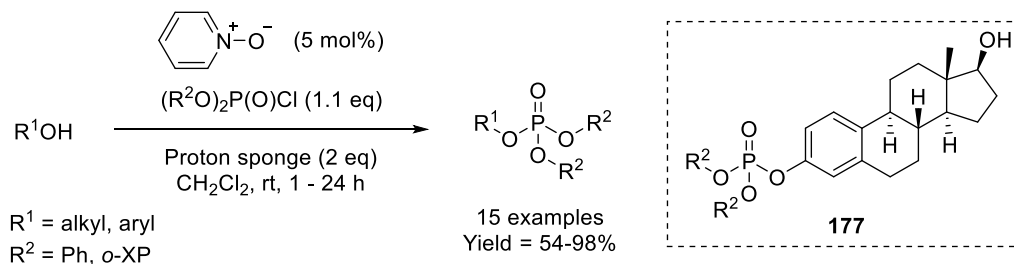
This methodology was subsequently applied to the synthesis of a series of dinucleoside monophosphate species **176** (Scheme 86).¹⁹⁶⁻¹⁹⁸ 4-Alkoxy derivatives of pyridine *N*-oxide were found to display the highest levels of catalytic activity for phosphotriester bond formation with the reaction proceeding to complete conversion within 30 seconds, whilst minimising the formation of any sulphur based by-products.¹⁹⁶⁻¹⁹⁸ However, the *N*-oxide is required in relatively large excess.¹⁹⁶⁻¹⁹⁸



Scheme 86. Synthesis of dinucleoside monophosphate species **176**.¹⁹⁶

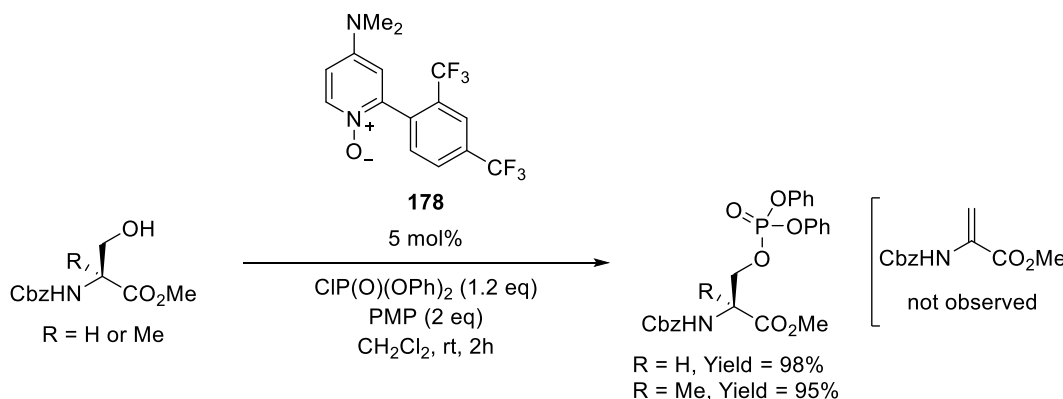
More recently, pyridine *N*-oxide was identified by Spivey *et al.* as an effective nucleophilic catalyst for the room temperature phosphorylation of alcohols with phosphoryl chlorides, namely diphenyl phosphoryl chloride (DPPCl) and *o*-xylenyl phosphoryl chloride (*o*-XPCl) (Scheme 87).¹⁹⁹ Notably, the use of such reagents circumvents the need for the sulfonyl chloride condensing agent and allows for the *N*-oxide to be employed in sub-stoichiometric quantities (5 mol%).¹⁹⁹ This methodology was amenable to a wide range of primary and secondary alcohols as well as phenols, with the desired phosphorylated species typically isolated in good yields (54-98%).¹⁹⁹ Owing to the lower reactivity of secondary and tertiary alcohols, chemoselective phosphorylation of primary and phenolic hydroxyl functionalities in the presence of more substituted alcohols was permissible, as observed for steroid derivative **177**.¹⁹⁹ NMR spectroscopic studies were again consistent with the *in situ* generation of *O*-phosphorylated salt

175 as the active phosphorylating species (Scheme 85), with expeditious conversion of an alcohol to the corresponding phosphotriester achieved by application of the isolated salt.¹⁹⁹



Scheme 87. Pyridine *N*-oxide catalysed phosphorylation of alcohols with DPPCl and *o*-XPCL.¹⁹⁹

2-Aryl-4-(dimethylamino)pyridine *N*-oxides, such as **178**, provided improved chemoselectivity within the phosphorylation of polyols and promoted catalytic phosphoryl transfer to hydroxyl amino acids (Table 2, Scheme 88).²⁰⁰ In the context of the latter, the weakly basic nature of the *N*-oxide organocatalyst provided a method suitable for substrates that are otherwise highly susceptible to subsequent elimination, such as serine (Scheme 88).²⁰⁰ Additionally, this method benefits from highly controllable chemoselectivity, with variations in the reaction conditions and phosphorylating agent altering the site of reaction within complex polyols (Table 2).²⁰⁰



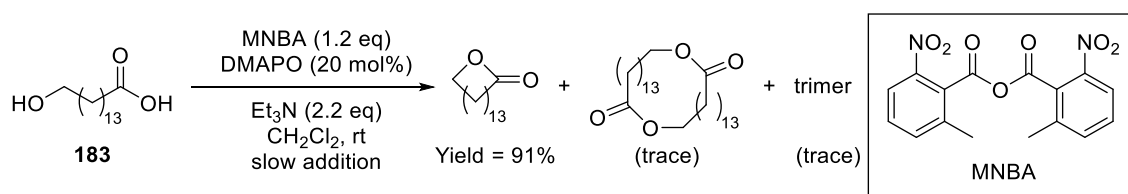
Scheme 88. Phosphorylation of serine and α -methylserine catalysed by aromatic *N*-oxide **178**.²⁰⁰

Table 2. Tuneable chemoselectivity within the phosphorylation of polyols catalysed by *N*-oxide **178**.²⁰⁰

				<p>179 R¹ = P, R² = H, R³ = H 180 R¹ = H, R² = H, R³ = P 181 R¹ = P, R² = H, R³ = P 182 R¹ = P, R² = P, R³ = P (where P = P(O)(OPh)₂ or o-XP)</p>			
Entry	Base/H ⁺ scavenger (eq)	Reaction time (h)	Phosphorylating agent (eq)	Product Yield (%)			
				179	180	181	182
1	PPO (2.0)	8	CIP(O)(OPh) ₂ (1.2)	94	<5	-	-
2	PMP (1.0)	1	<i>o</i> -XPCI (1.0)	11	81	-	-
3	PMP (2.2)	4	CIP(O)(OPh) ₂ (2.2)	<5	<5	86	-
4	PS [®] (3.2)	24	CIP(O)(OPh) ₂ (3.2)	-	-	<5	96

1.4.4 Acylation reactions

In 2002, Shiina and co-workers determined that DMAPO can successfully be employed as an alternative organocatalyst for the macrolactonisation of ω -hydroxycarboxylic acids **183**, with 2-methyl-6-nitrobenzoic anhydride (MNBA) as the coupling reagent (Scheme 89).²⁰¹ This protocol, which was also found to help limit formation of undesired dimer and trimer based macrocycles, was then examined within the preparation of protected *erythro*-aleuritic acid lactone **184**, a key intermediate in the synthesis of (9*E*)-isoambrettolide, with **184** generated in 90% yield (Figure 20).^{201,202} Applying slight modifications, this methodology was then extended to the synthesis of two further natural products; octalactin **185** and (-) and (+)-2-hydroxy-24-oxooctacosanolide **186**, with the key lactonisation steps affording the cyclic products in good yields of 90% and 77% respectively (Figure 20).^{203,204}

**Scheme 89.** DMAPO promoted lactonisation of ω -hydroxycarboxylic acid **183**.²⁰¹

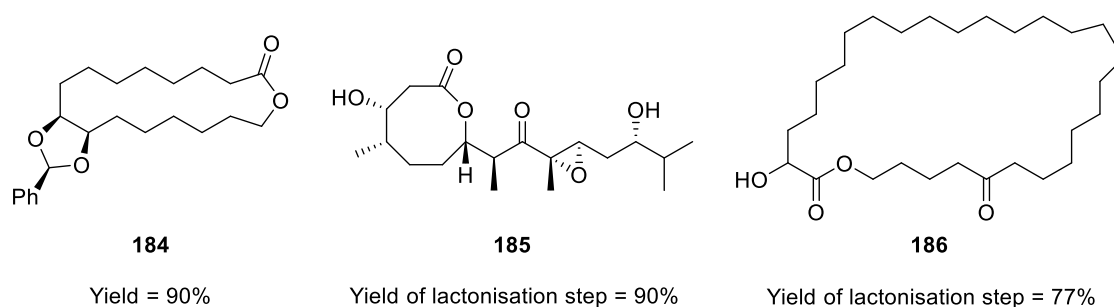
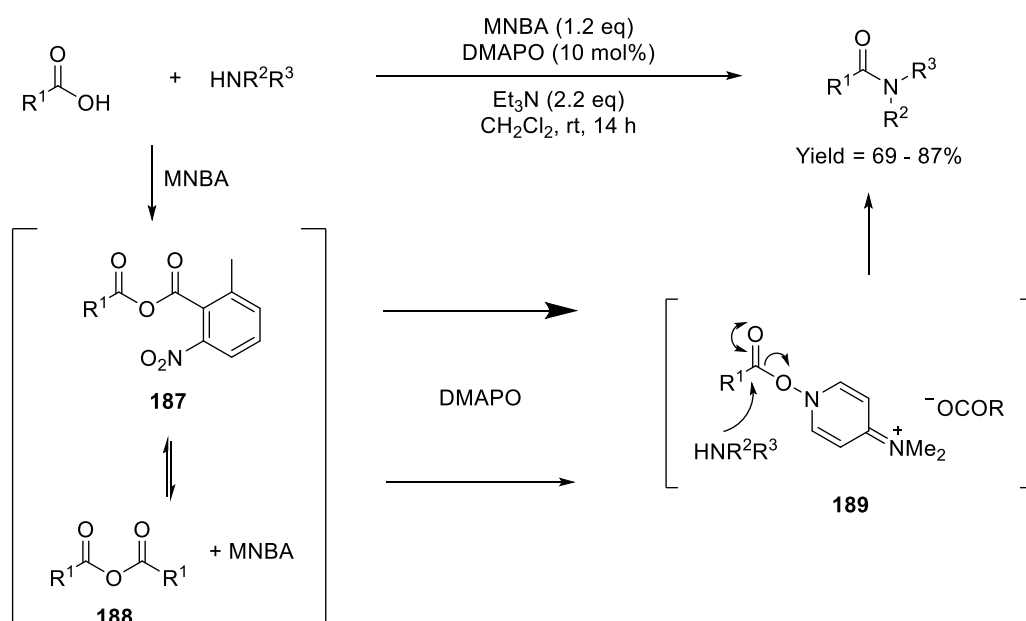


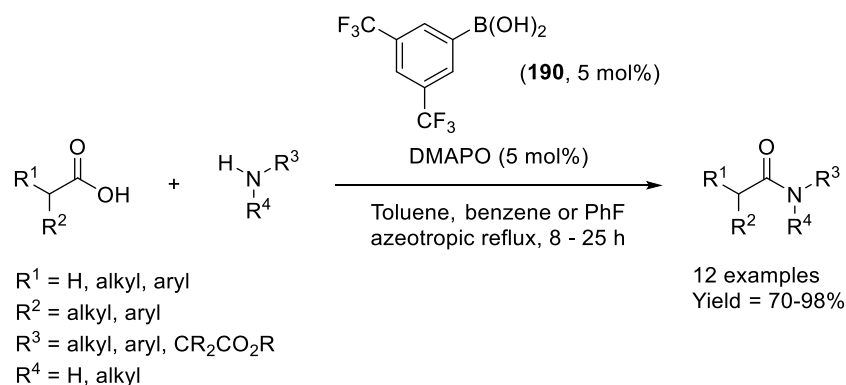
Figure 20. Lactones synthesized according to the developed acylation methodology.^{201,203,204}

More recently, Shiina *et al.* have reported that amide bonds and peptides can also be synthesized using this procedure, by simply substituting the alcohol based nucleophile for an amine or α -amino acid respectively.²⁰⁵ Typically, these coupling reactions are high yielding, employ extremely mild conditions and are effective at reduced catalyst loadings (10 mol%) (Scheme 90).²⁰⁵ The authors have postulated that the reaction proceeds *via* the mechanism shown in Scheme 90 and that the role of the DMAPO is to form highly reactive pyridinium salts **189** that are subject to nucleophilic attack.²⁰⁵ Initially, it is believed that, in the presence of DMAPO and triethylamine, mixed anhydride **187** is formed upon condensation of the carboxylic acid with MNBA, as evidenced by ¹H NMR spectroscopic studies.^{201,205} Furthermore, it was determined that anhydride **187** exists in equilibrium with methoxyacetic anhydride **188** and both anhydride species are believed to react with DMAPO to generate activated species **189**. Reaction of these pyridinium salts (**189**) with an amine nucleophile then generates the required amide.^{201,205} It is conceivable that a similar mechanism is operating for lactonisation reactions, with nucleophilic attack by an alcohol generating the desired cyclic lactone.^{201,205}

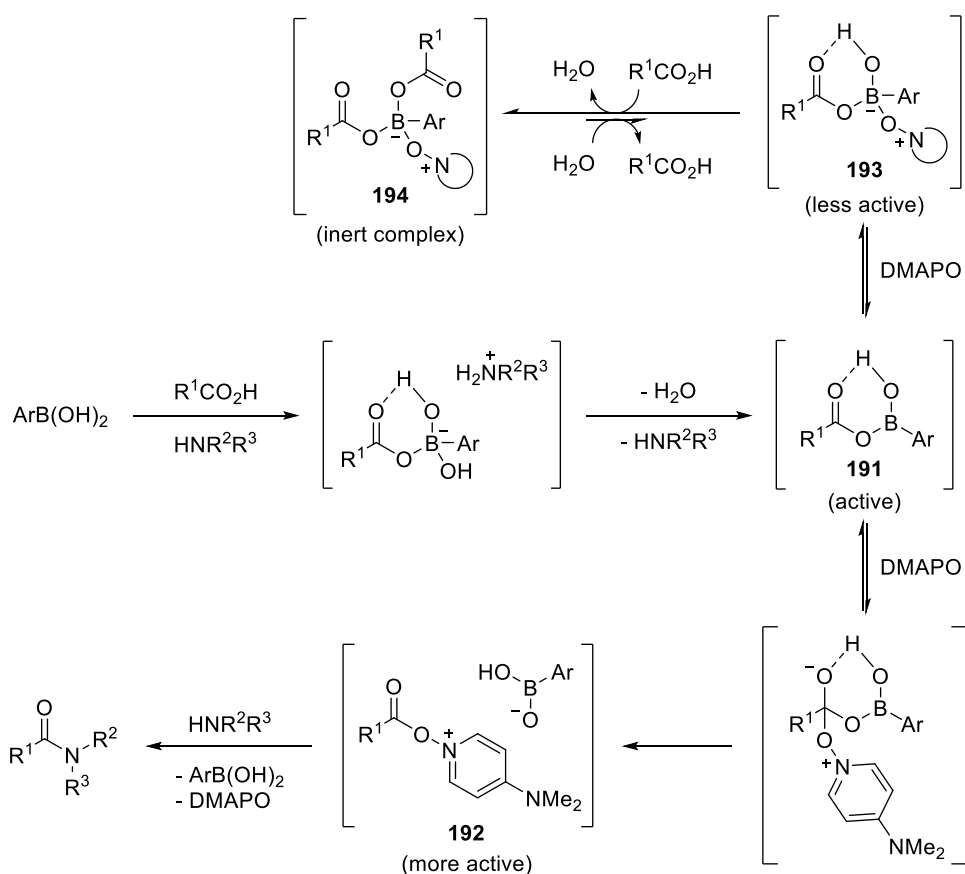


Scheme 90. Mechanism for the *N*-oxide promoted synthesis of amides from carboxylic acids.²⁰⁵

In 2016, Ishihara and Lu demonstrated that the direct condensation of carboxylic acids with amines to afford the corresponding amides was subject to cooperative catalysis by arylboronic acids and DMAPO, with a synergistic effect noted (Scheme 91).²⁰⁶ Under anhydrous conditions (azeotropic reflux or employing molecular sieves), initial activation of the carboxylic acid *via* formation of mixed anhydride **191** with the arylboronic acid was proposed (Scheme 92).²⁰⁶ It was suggested that the role of the nucleophilic *N*-oxide additive was to form the more reactive cationic intermediate **192**, which is analogous to the salt (**189**) proposed by Shiina *et al.* albeit with a different counter ion.²⁰⁶ Excellent yields were reported for the amidation of α -branched carboxylic acids and arenecarboxylic acids with amines of varying steric bulk and nucleophilicity using boronic acid **190** as the Lewis acidic component (70-98%).²⁰⁶ Alternatively, for the more reactive α -nonbranched carboxylic acids, formation of complex **193** and subsequent acylation to generate **194**, which is inert to amidation, became increasingly competitive.²⁰⁶ Complexes of the form **194**, in which the *N*-oxide is coordinated to the boron, were even isolated for those carboxylic acids of reduced steric requirement.²⁰⁶ Thus, to achieve preferential formation of **192**, boronic acids of reduced Lewis acidity and increased steric bulk were required.²⁰⁶ Specifically, phenylboronic acid (or *o*-substituted derivative: 2-iodo-5-methoxyphenyl boronic acid) in conjunction with DMAPO were found to constitute successful amidation catalysts for the condensation of α -nonbranched carboxylic acids, affording the corresponding amides in excellent yields.²⁰⁶



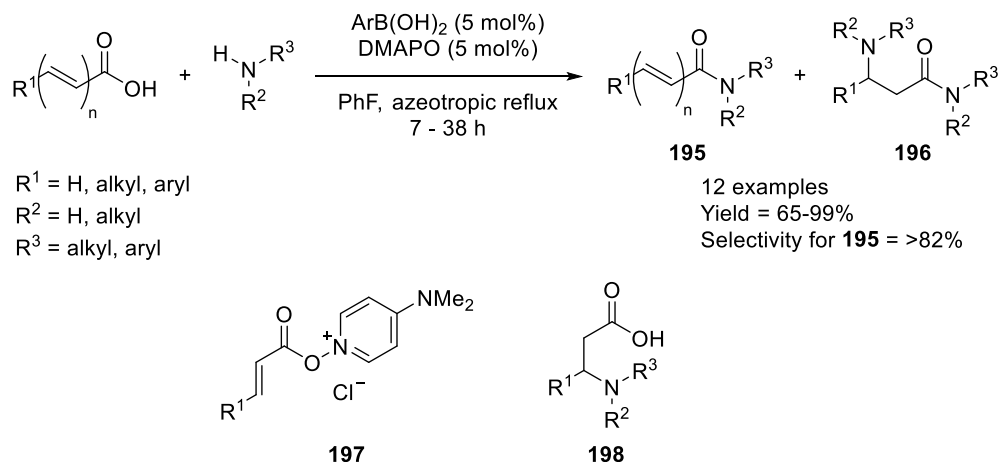
Scheme 91. Cooperative catalysis by arylboronic acids and DMAPO for the direct condensation of carboxylic acids with amines.²⁰⁶



Scheme 92. Proposed mechanism for the activation of carboxylic acids towards dehydrative condensation with amines.²⁰⁶

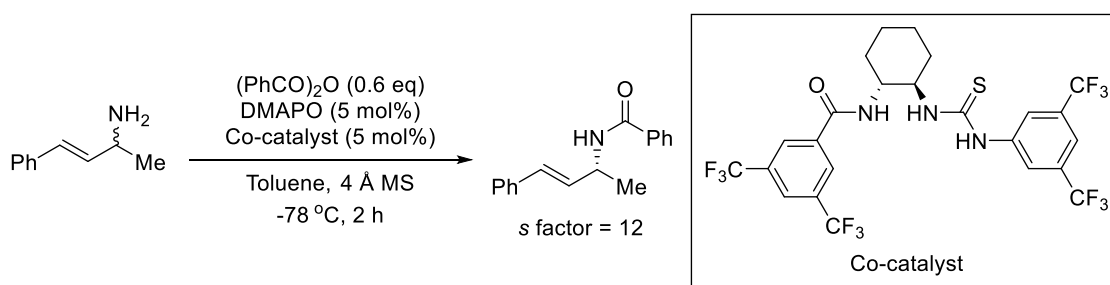
Improved chemoselectivity and yields were also reported for the amidation of β -substituted acrylic acids and other conjugated carboxylic acids utilising the devised cooperative catalytic approach relative to the boronic acid alone (Scheme 93).²⁰⁶ The authors provided evidence for the formation of cationic intermediate **197**, with treatment of the pre-prepared salt with an amine generating exclusively the expected amide **195**.²⁰⁶ Formation of Michael addition product **196** was minimised in the presence of the *N*-oxide, which was proposed to form *via* initial

1,4-conjugate addition of the amine nucleophile to the starting material to generate intermediate **198** rather than from the product (**195**).²⁰⁶

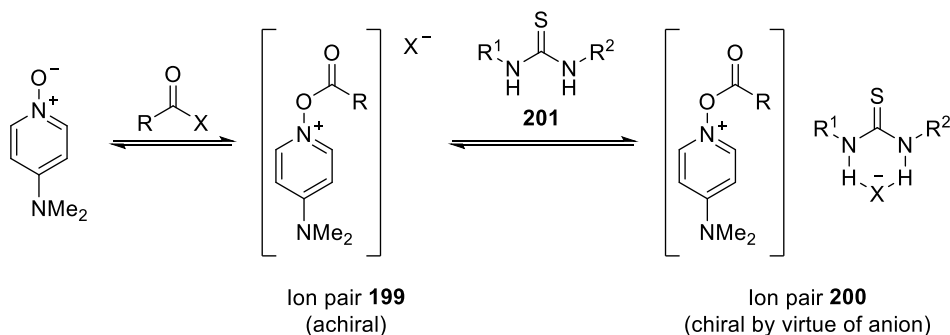


Scheme 93. Amidation of β -substituted acrylic acids and other conjugated carboxylic acids in the presence of the cooperative catalytic system.²⁰⁶

Complementary to these reports, Seidel *et al.* have published some preliminary results indicating the potential use of DMAPO as part of a dual catalytic system for the kinetic resolution of allylic amines (Scheme 94).²⁰⁷ In line with previous proposals, it is believed that the DMAPO is initially acylated to form intermediate **199**, which can then form chiral ion pair **200** through hydrogen bond interactions with the chiral anion receptor **201** (Scheme 95).²⁰⁷ As the chiral ion pair exhibits enhanced reactivity towards nucleophilic attack by the racemic amine, this methodology allows for kinetic resolution of the amine enantiomers to be achieved.²⁰⁷

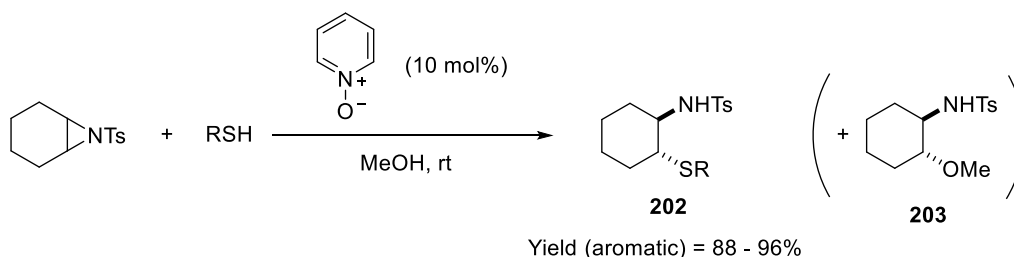


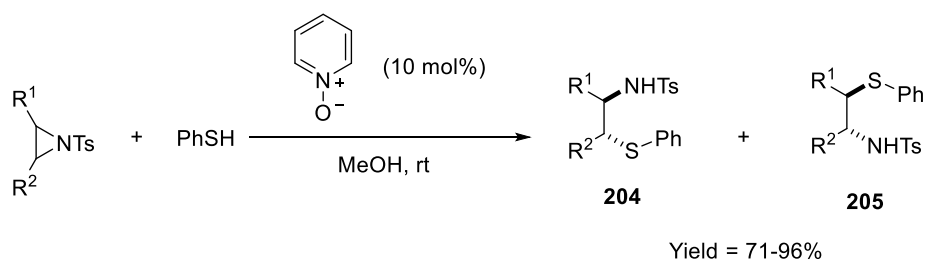
Scheme 94. Kinetic resolution of allylic amines using N-oxides.²⁰⁷

Scheme 95. Formation of activated chiral ion pair **200**.²⁰⁷

1.4.5 Ring opening of aziridines

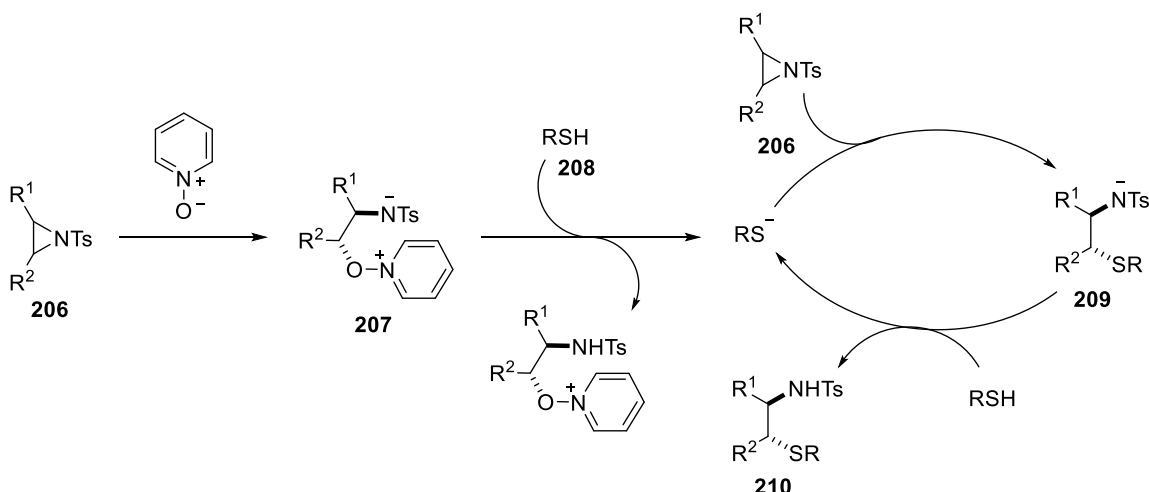
Yiyuan and co-workers demonstrated that pyridine *N*-oxide can successfully be employed as an organocatalyst for the ring opening of aziridines by thiols.²⁰⁸ The β -amino sulphides provided, which were shown to possess *anti*-stereochemistry, are useful synthetic intermediates for many biologically active compounds.²⁰⁸ Although good to excellent yields of **202** were attained for a range of aromatic thiols (88 - 96%), the ring-opened product **203** was generated using aliphatic thiols (23 - 25%), which is formed due to competing nucleophilic attack of the aziridine by the methanol solvent (Scheme 96).²⁰⁸ The authors reported that by substituting methanol for tetrahydrofuran or acetonitrile, the desired product **202** could be formed preferentially, albeit in low yields (10 - 12%).²⁰⁸ With regards to the aziridine, the substrate scope and functional group compatibility were found to be excellent (Scheme 97), and for unsymmetrical substrates the regioselectivity of the reaction proved to be relatively high (regioselectivity **204**:**205**: 25:75 - 96:4, yield: 71 - 96%).²⁰⁸ Typically, the aziridine reacts with the thiol at the least substituted carbon, with the exception of aziridines bearing an aromatic group; for which thiolysis occurs at the benzylic aziridine carbon.²⁰⁸

Scheme 96. PNO catalysed ring opening reaction of aziridines with thiols.²⁰⁸



Scheme 97. PNO catalysed ring opening reaction of aziridines with benzenethiol.²⁰⁸

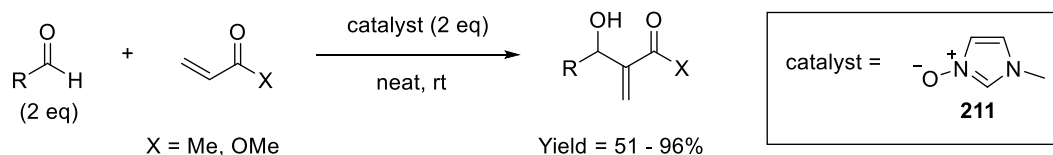
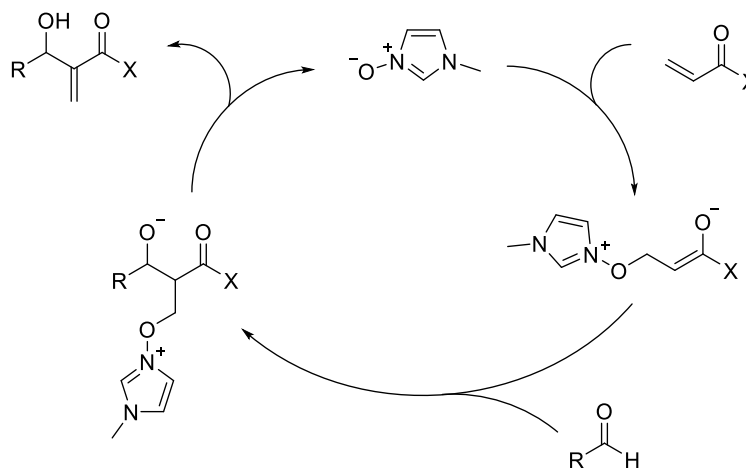
It has been postulated that the reaction follows the general mechanism shown in Scheme 98.²⁰⁸ The role of the *N*-oxide is to initiate the reaction by attacking aziridine **206** to afford intermediate **207**, which can then deprotonate thiol **208** to form the more nucleophilic species RS^- , which is part of the catalytic cycle.²⁰⁸ RS^- then participates in the thiolysis of aziridine **206** to afford the second ring-opened intermediate **209**.²⁰⁸ Deprotonation of a further thiol molecule by **209** results in the formation of the desired β -amino sulphide **210** and regenerates RS^- .²⁰⁸



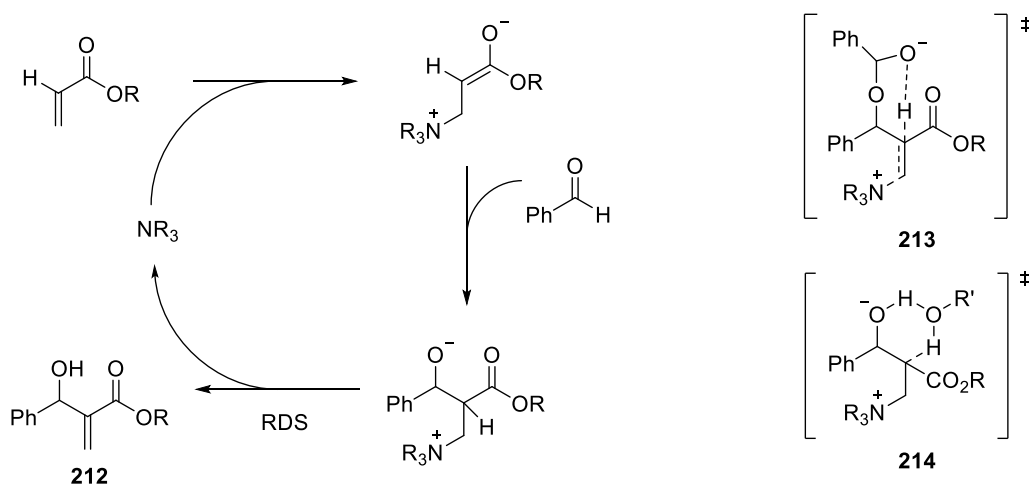
Scheme 98. Proposed mechanism for the PNO catalysed ring opening of aziridines with thiols.²⁰⁸

1.4.6 Morita-Baylis-Hillman reaction

N-Oxides have also found application as organocatalysts within the Morita-Baylis-Hillman (MBH) reaction.²⁰⁹⁻²¹⁴ Preliminary studies conducted by Tsai *et al.* demonstrated that 1-methylimidazole 3-*N*-oxide (**211**) can catalyse the MBH reaction of activated alkenes, namely methyl vinyl ketone and methyl acrylate, with numerous aldehydes under solvent free conditions (Scheme 99).²⁰⁹ Although it was found that employing two equivalents of *N*-oxide **211** was optimal, the mechanism proposed by Tsai and co-workers indicates that the *N*-oxide is regenerated within the reaction and participates as part of the catalytic cycle shown in Scheme 100.²⁰⁹

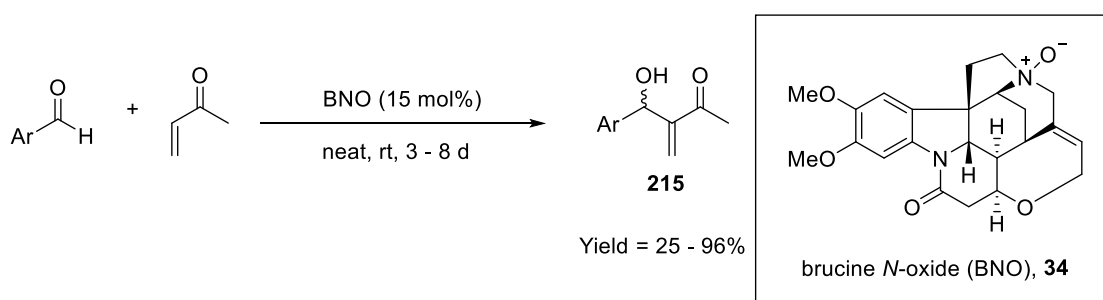
Scheme 99. MBH reaction promoted by *N*-oxide **211**.²⁰⁹Scheme 100. Proposed mechanism for the *N*-oxide promoted MBH reaction.²⁰⁹

The groups of McQuade and Aggarwal/Lloyd-Jones have independently reported that α -proton transfer to generate **212** is the rate-determining step, at least during the early stages of the reaction, as a primary kinetic isotope effect was recorded at this position (Scheme 101).²¹⁰⁻²¹⁴ For systems that do not involve polar protic solvents, McQuade and co-workers have demonstrated that the reaction is second order with respect to the aldehyde.^{210,212,213} In order to account for this observation, the authors have proposed that a further aldehyde reacts with the alkoxide species to generate hemiacetal intermediate **213**, which is believed to aid subsequent elimination of the catalytic species during the slow step of the reaction.^{210,212,213} However, in the presence of an alcohol, Aggarwal and co-workers have gathered evidence to suggest that rate determining proton transfer proceeds *via* the intermediate **214**.²¹¹⁻²¹³ It should be noted that these mechanistic studies were performed on related amine catalysed systems, however it may be anticipated that these findings can be directly applied to the *N*-oxide catalysed MBH reaction.²¹⁰⁻²¹⁴



Scheme 101. Proposed transition states for the rate determining step of the MBH reaction.^{211,214}

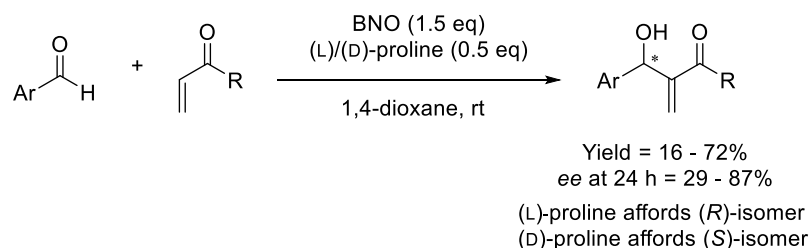
The first truly catalytic variant of the *N*-oxide promoted MBH reaction was published by Oh and co-workers in 2010, which, in accordance with Tsai *et al.*, was proposed to proceed *via* 1,4-conjugate addition of the *N*-oxide to an α,β -unsaturated ketone.^{209,213} Specifically, this system employs brucine *N*-oxide (**34**) as the organocatalyst and was found to promote the reaction of methyl vinyl ketone with aromatic aldehydes with varying degrees of success (Scheme 102).²¹³ As previously observed by Tsai *et al.*, the reaction is sensitive to the electronics of the aldehyde substrate, with the highest yields being generated for electron deficient substrates.^{209,213} It is interesting to note that once an appreciable amount (> 10%) of product **215** has been formed, it can act synergistically with *N*-oxide **34** to catalyse the reaction.²¹³ This phenomenon may be attributed to the protic nature of species **215**, which allows it to promote the slow hydrogen abstraction step in a manner consistent with that proposed by Aggarwal *et al.*^{211,213}



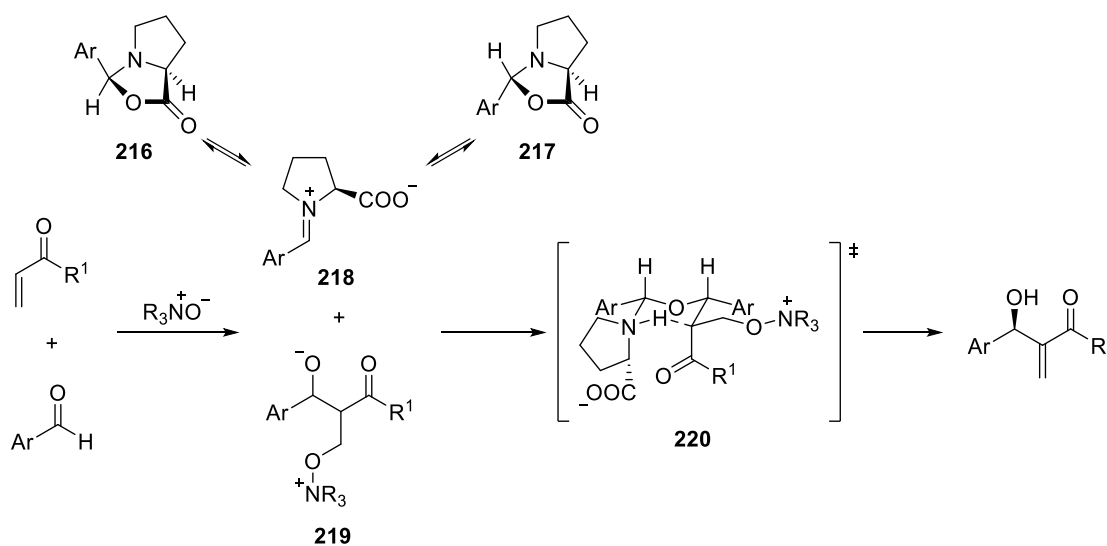
Scheme 102. BNO catalysed MBH reaction of methyl vinyl ketone with aromatic aldehydes.^{213,214}

Subsequently, a cooperative catalysis system, consisting of BNO and proline, was developed by Oh *et al.* to mediate an asymmetric MBH reaction.^{213,214} As can be seen from Scheme 103, moderate to good enantioselectivities were attained for a range of aromatic aldehydes using the optimised methodology.^{213,214} However, the *N*-oxide could no longer be employed in substoichiometric quantities.²¹³ Nevertheless, the mechanistic findings are of particular interest.²¹³ *In situ* ¹H NMR studies of the crude reaction mixture revealed the formation of *endo*- and

exo-oxazolidinone isomers **216** and **217** (Scheme 104).²¹³ Oh *et al.* believe that this is indicative of iminium species **218** being formed as an intermediate in this MBH reaction, which, upon reaction with the activated vinyl ketone species **219** can afford *N,O*-hemiacetal **220**.^{213,214} The rate determining proton-transfer step is believed to occur *via* 6 membered cyclic intermediate **220**, with the proline fragment affording stereocontrol.^{213,214} Oh and co-workers have postulated that brucine *N*-oxide may also play a role in stabilising iminium species **218**, however the precise mode of catalysis remains undetermined.^{213,214}



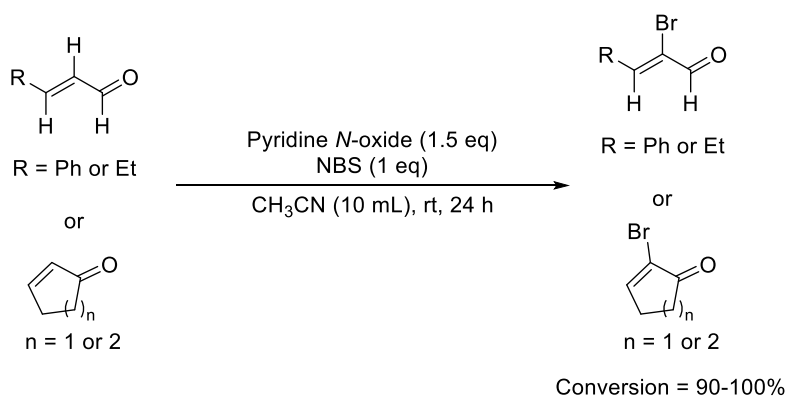
Scheme 103. BNO / proline catalysed enantioselective MBH reaction.²¹³



Scheme 104. Mechanism of the BNO / proline catalysed enantioselective MBH reaction.^{213,214}

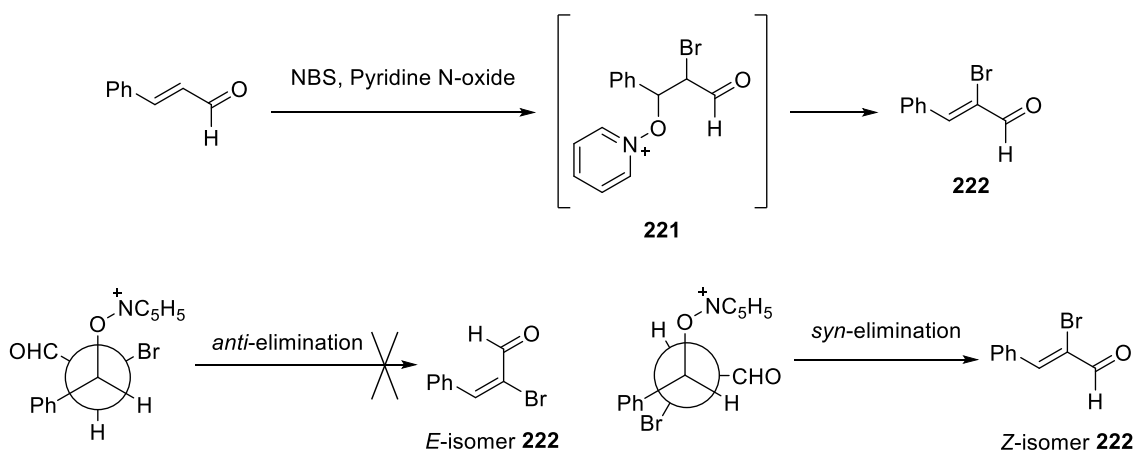
1.4.7 Halogenation reactions

In 2007 Bovonsombat and co-workers showed that, in stoichiometric quantities, pyridine *N*-oxide could successfully promote the α -bromination of cyclic enones and linear enals with *N*-bromosuccinimide at room temperature (Scheme 105).²¹⁵ High conversion and selectivity was achieved for the small sample of substrates examined (90-100% conversion, 100% selectivity) and undesirable oxidation of the aldehyde functionality was avoided.²¹⁵



Scheme 105. PNO promoted α -bromination of linear enals and cyclic enones with NBS.²¹⁵

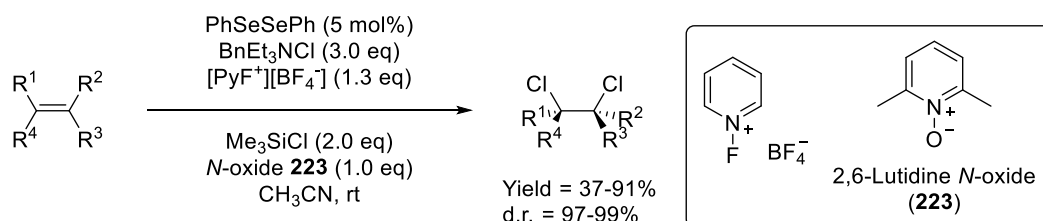
In this example, the *N*-oxide is again proposed to function as a nucleophilic catalyst; generating **221** as a key intermediate (Scheme 106).²¹⁵ It may be envisaged that this intermediate is formed *via* either 1,4-conjugate addition of the *N*-oxide to the substrate forming an enolate, which is capable of abstracting bromine, or alternatively through the formation of a bromonium species, which may be ring opened by the *N*-oxide.²¹⁵ Intermediate **221** can subsequently undergo elimination to afford the corresponding α -brominated product (**222**).²¹⁵ Interestingly, this reaction occurs with retention of the olefin geometry, with *trans*-enals affording exclusively the *Z*-isomer of the α -brominated product.²¹⁵ This stereochemical outcome has been attributed to *syn*-elimination of the α -hydrogen and *N*-oxide species from **221** (Scheme 106).²¹⁵



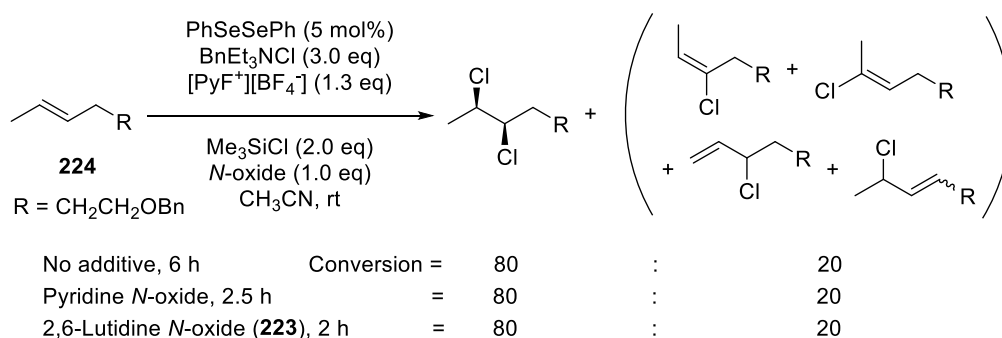
Scheme 106. Mechanism and stereochemical rationale for the PNO promoted bromination of *trans*-enals with NBS.²¹⁵

In 2016, pyridine *N*-oxide and 2,6-lutidine *N*-oxide (**223**) were identified by Denmark *et al.* as particularly efficient Lewis basic additives for promoting the organoselenium catalysed stereospecific *syn*-dichlorination of alkenes, using benzyltriethylammonium chloride as the chloride source (Scheme 107).²¹⁶ Specifically, for the *syn*-dichlorination of (*E*)-1-benzyloxy-4-hexene (**224**), the reaction time was reduced from 6 hours to 2 hours in the

presence of 1 equivalent of 2,6-lutidine *N*-oxide, whilst the extent of the reaction and distribution of products remained unchanged (Scheme 108).²¹⁶ This methodology was applied to numerous acyclic and cyclic substrates, with high diastereoselectivities (>97% d.r.) universally achieved and where examined a similar rate enhancement was observed.²¹⁶ However, *N*-oxides were found to be incompatible with allylic alcohols, for which numerous by-products were formed. Nevertheless, the corresponding products were still accessible in good yield (66-76%) with exclusion of the additive.²¹⁶



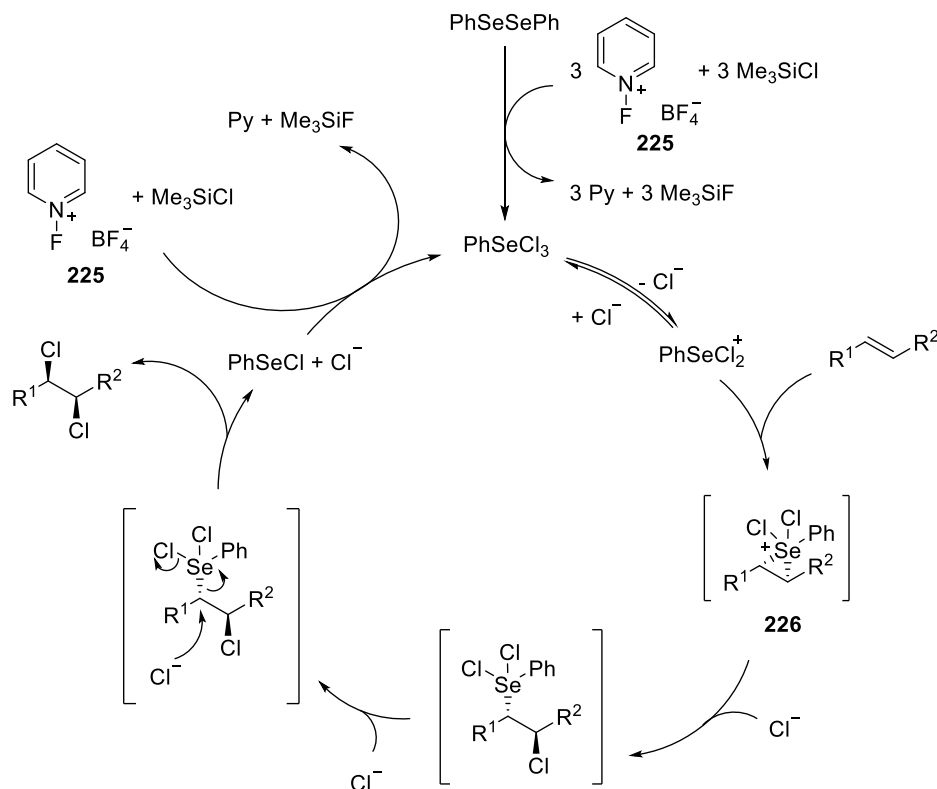
Scheme 107. 2,6-Lutidine *N*-oxide as a Lewis basic additive for accelerating the organoselenium catalysed stereospecific *syn*-dichlorination of alkenes.²¹⁶



Scheme 108. Effect of aromatic *N*-oxide additives on the reaction rate and selectivity for the *syn*-dichlorination of (*E*)-benzyloxy-4-hexene (**224**).²¹⁶

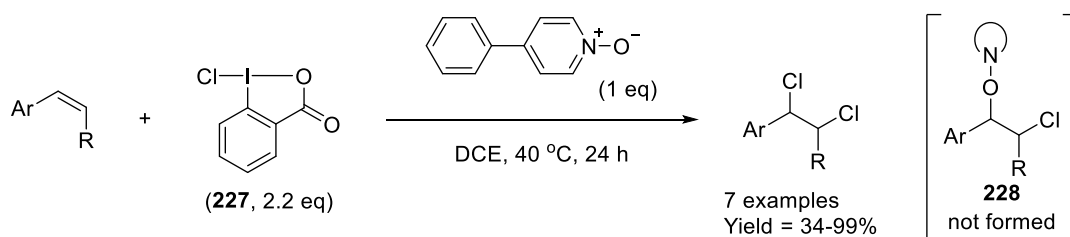
Whilst several potential alternatives were also provided, the authors have tentatively proposed that the reaction may proceed *via* the catalytic cycle shown in Scheme 109.²¹⁶ Notably, *N*-fluoropyridinium salt **225** is employed as an oxidant to produce the active catalyst, PhSeCl₃, which reacts with the alkene to form three membered cyclic intermediate **226**, potentially with prior loss of a chloride ion.²¹⁶ The dichlorinated product is then generated *via* ring opening of the seleniranium ion followed by displacement of the selenium fragment.²¹⁶ Crucially, in both instances these processes proceed *via* an S_N2 mechanism with a chloride ion; which imparts the *syn*-diastereoselectivity observed.²¹⁶ Insight into the role of the *N*-oxide additive has not been provided by the authors, as the rate determining step is yet to be determined.²¹⁶ However, it has been ascertained that the *N*-oxide is not acting as the oxidising agent, as the reaction does not proceed in the absence of *N*-fluoropyridinium salt **225**.²¹⁶ Additionally, it was reported that only the background *anti*-dichlorination could be obtained without the organoselenium pre-catalyst.²¹⁶

This indicates that the *N*-oxide is not a factor in determining the stereoselectivity and interestingly the *N*-oxide also does not enhance the rate of the *anti*-dichlorination reaction.²¹⁶

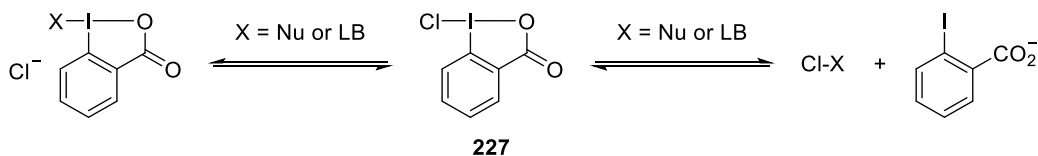


Scheme 109. Proposed mechanistic cycle for the organoselenium catalysed stereospecific *syn*-dichlorination of alkenes with benzyltriethylammonium chloride.²¹⁶

Whilst examining the suitability of Togni's reagent (**227**) as an electrophilic chlorination reagent, Egami and co-workers determined that the dichlorination of alkenes could be promoted in aprotic solvents in the presence of stoichiometric quantities of 4-phenylpyridine *N*-oxide (Scheme 110).²¹⁷ Specifically, the dichlorination of a series of styrene derivatives was examined, with superior yields obtained for *para*-substituted electron rich species (69-99%).²¹⁷ *o*-OMe and *p*-Cl analogues were isolated in poorer yields (50% and 34% respectively) alongside the 2-chlorostyrene derivative and limited success was reported for a less reactive aliphatic substrate (35% yield).²¹⁷ By virtue of this reactivity sequence, chemoselective dichlorination of a styryl moiety in the presence of an aliphatic olefin and a more sterically encumbered conjugated alkene could be achieved.²¹⁷ As observed for other nucleophiles, the authors originally anticipated the formation of *N*-oxide adduct **228**, which would undergo elimination to afford α -chloroketones.²¹⁷ Thus, based on the nature of the product formed, the *N*-oxide is proposed to instead generate a more electrophilic source of chlorine by interacting with reagent **227**, with the second chloride being liberated *via* ligand exchange with the *N*-oxide (Scheme 111).²¹⁷

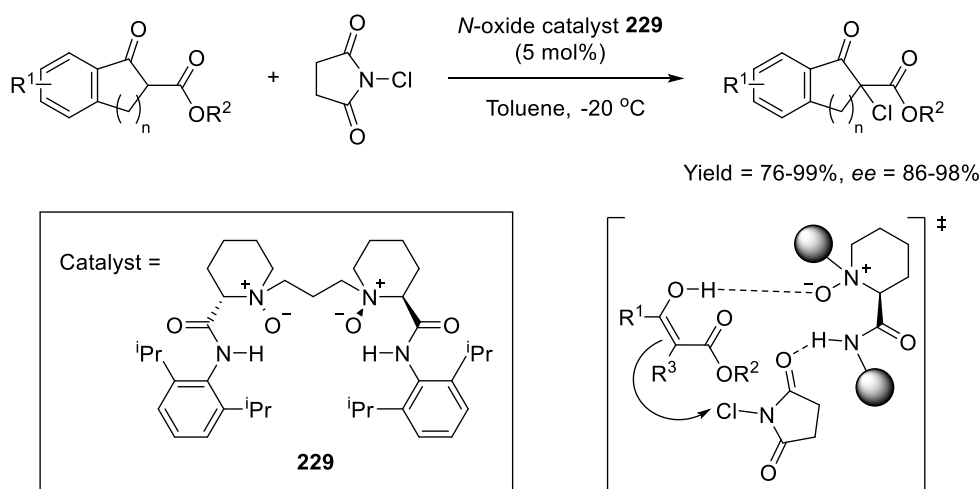


Scheme 110. 4-Phenylpyridine *N*-oxide promoted dichlorination of alkenes with Togni's reagent **227**.²¹⁷



Scheme 111. Proposed modes of activation of Togni's reagent **227**.²¹⁷

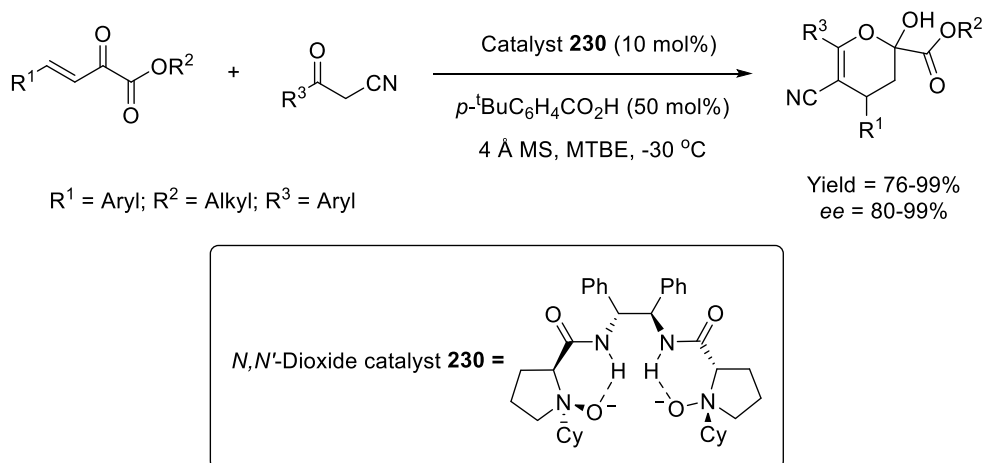
As previously detailed, C2-symmetric *N,N'*-dioxides have found application within the field of asymmetric catalysis; functioning as organocatalysts within organosilicon chemistry and as chiral ligands to promote a variety of stereoselective transformations.² A comprehensive review has recently been published by Liu *et al.* on this topic.² Whilst *N,N'*-dioxides typically function as Lewis basic, nucleophilic catalysts in the context of organosilicon chemistry to activate the silicon centre, it has also been reported that bifunctional *N,N'*-dioxides can promote asymmetric transformations *via* hydrogen bond catalysis.²¹⁸⁻²²⁰ For instance, Feng *et al.* developed *N,N'*-dioxide **229** as an organocatalyst for the *N*-chlorosuccinimide (NCS) mediated enantioselective α -chlorination of cyclic β -ketoesters (Scheme 112).^{2,218} A range of cyclic α -chloro- β -ketoesters were successfully synthesized in good to excellent yields (76-99%) and excellent enantioselectivity (86-98% *ee*) using this methodology, with extremely low catalyst loading required (5 mol%).²¹⁸ Tuning of the sterics, linker length and identity of the *N*-oxide ring fragment was found to be essential for achieving such high enantioselectivity.²¹⁸ Interestingly, the corresponding parent amine induced much lower levels of asymmetric control.²¹⁸ It has since been proposed that the *N*-oxide functionality serves to activate the enol tautomer of the β -ketoester by functioning as a hydrogen bond acceptor, whilst the NH of the amide moiety simultaneously enhances the electrophilicity of the NCS *via* hydrogen bond donation.^{2,218}



Scheme 112. *N,N'*-Dioxide promoted asymmetric α -chlorination of cyclic β -ketoesters with *N*-chlorosuccinimide.^{2,218}

1.4.8 Asymmetric tandem Michael reactions

Feng and co-workers subsequently reported that bifunctional *N,N'*-dioxide **230** effectively promotes the synthesis of chiral dihydropyrans from α -substituted cyano ketones and β,γ -unsaturated α -ketoesters *via* an asymmetric tandem Michael-hemiacetalisation reaction (Scheme 113).²¹⁹ The developed methodology was found to be amenable to a wide range of substrates and was insensitive to the electronics of the aromatic substituents at R^1 and R^3 ; universally achieving excellent yields (76-99%) and enantioselectivities (80-99% *ee*).²¹⁹ Interestingly, the best results were attained when the aromatic group at R^1 was *ortho*-substituted, whilst some success was achieved with an aliphatic group at the R^1 position using vastly extended reaction times.²¹⁹ Bifunctional catalyst **230** is thought to function in an analogous manner to that outlined above for the α -chlorination reaction, with the proposed transition state for initial Michael addition shown in Figure 21.²¹⁹



Scheme 113. *N,N'*-Dioxide catalysed asymmetric tandem Michael-hemiacetalisation reaction of α -substituted cyano ketones with β,γ -unsaturated α -ketoesters.²¹⁹

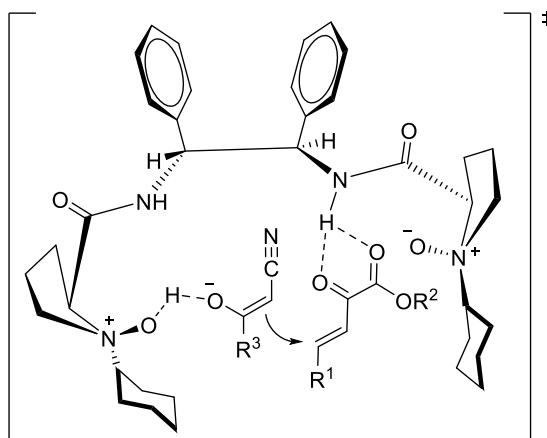
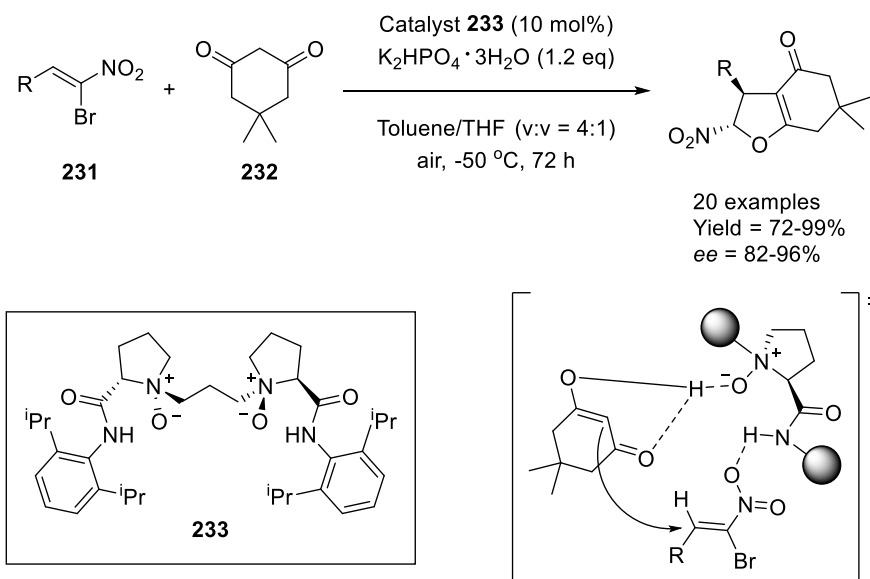


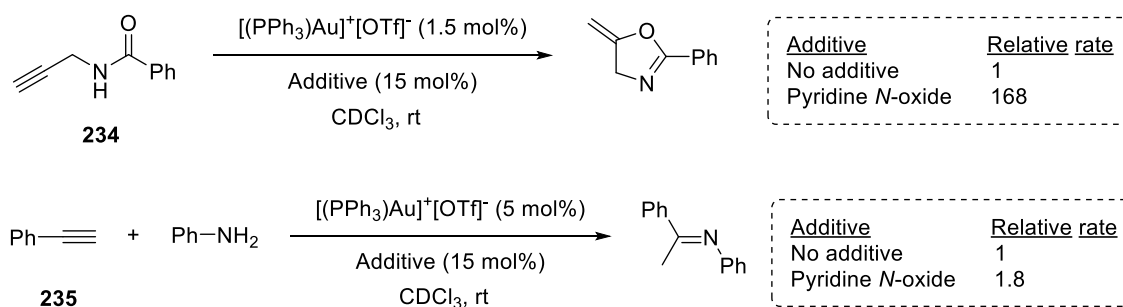
Figure 21. Proposed transition state for initial Michael addition.²¹⁹

Similarly, bifunctional catalyst **233** simultaneously activates both the enolate and bromonitrostyrene components within the asymmetric domino Michael-alkylation reaction *via* hydrogen bonding with the *N,N'*-dioxide and amide (N-H) fragments respectively (Scheme 114).²²⁰ This methodology was applied by Feng and co-workers to the synthesis of polysubstituted bicyclic dihydrofurans, for which the steric bulk of the *o*-isopropyl groups of catalyst **233** were found to impart superior enantioselectivities.²²⁰ Good to excellent yields and enantioselectivities (72-99% yield, 82-96% *ee*) were achieved from the reaction of numerous aryl substituted (*Z*)-bromonitrostyrenes (**231**) with dimedone (**232**).²²⁰ Alternatively, dihydrofurans containing three stereogenic centres were accessed in good yields and selectivities (71-90% yield, $\geq 75:25$ d.r., 82-94% *ee*) from 5-monosubstituted cyclohexane-1,3-diones *via* a Michael-alkylation reaction with (*Z*)-bromonitrostyrenes.²²⁰

Scheme 114. *N,N'*-Dioxide **233** catalysed asymmetric domino Michael-alkylation reaction.²²⁰

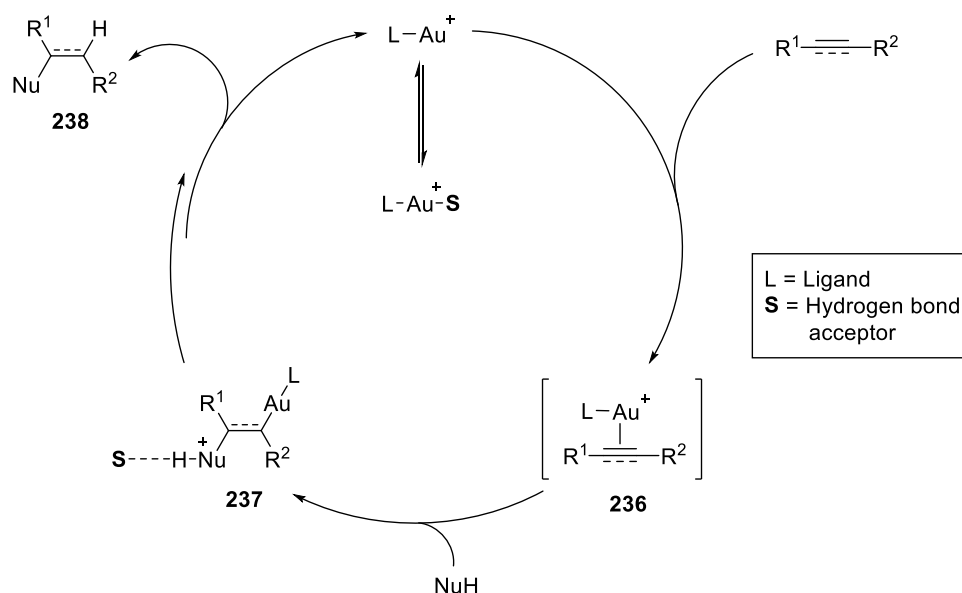
1.4.9 *N*-Oxides as additives within gold catalysed reactions

Most recently, simple *N*-oxide species have been reported as efficient hydrogen bond catalysts.^{221,222} Among other strong hydrogen bond acceptors, pyridine *N*-oxide was reported by Hammond, Xu and co-workers as an exceptional additive for improving the efficacy of the gold catalysed intramolecular cyclisation of propargyl amide **234** and the intermolecular hydroamination of alkynes (**235**) (Scheme 115).²²¹ Incredibly, for the former transformation the initial rate of cyclisation was calculated to be 168 times faster in the presence of only 15 mol% of the *N*-oxide additive relative to the background, whilst the initial rate of reaction for hydroamination was 1.8 times faster.²²¹ However, due to their relatively aurophilic nature, *N*-oxides were not found to be universally suitable additives for all of the gold catalysed transformations examined and in some instances even retarded the reaction rate.²²¹ In addition to pyridine *N*-oxide, benzotriazole was also identified as a promising additive for the transformations detailed.²²¹



Scheme 115. Effect of pyridine *N*-oxide on the rate of gold catalysed transformations.²²¹

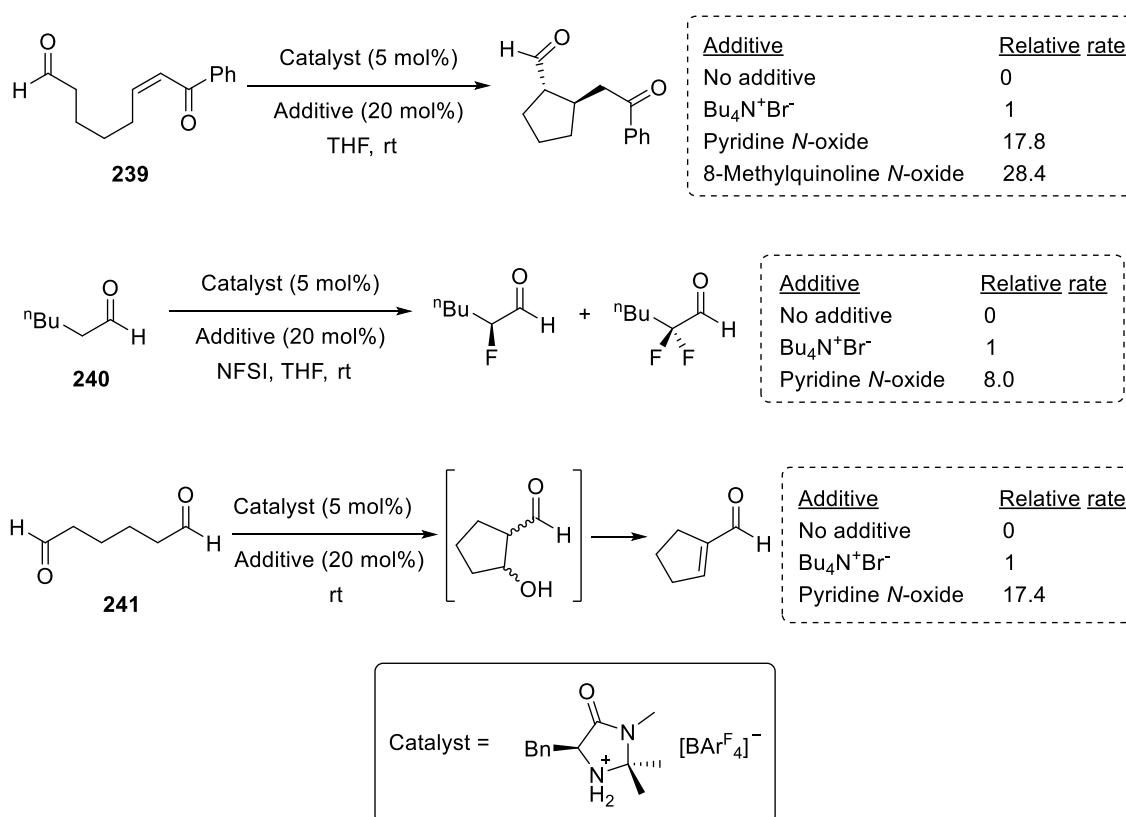
Homogeneous gold catalysed processes of this kind are considered to entail two key stages.^{221,223} Initially, nucleophilic attack of an η^2 -alkyne/alkene gold complex (**236**) generates cationic intermediate **237**, which subsequently undergoes protodeauration in the second stage to produce the desired product **238** and regenerate the gold catalyst (Scheme 116).^{221,223} In cases where the alkenyl bears good π -acceptors or the nucleophile contains a particularly basic moiety, a more stable cationic intermediate (**237**) will be formed, with some such species even being isolable.^{221,224} The cationic nature of **237** consequently impedes the approach of a proton required to achieve protodeauration; retarding the rate of the second stage and often rendering it rate determining.²²¹ Therefore, pyridine *N*-oxide is proposed to accelerate the rate of reaction by functioning as a hydrogen bond acceptor to aid proton transfer; reducing the cationic nature of the intermediate and consequently facilitating protodeauration.²²¹



Scheme 116. Proposed role of *N*-oxides and other hydrogen bond acceptors within homogeneous gold catalysed processes.²²¹

1.4.10 *N*-Oxides as additives within enamine catalysis

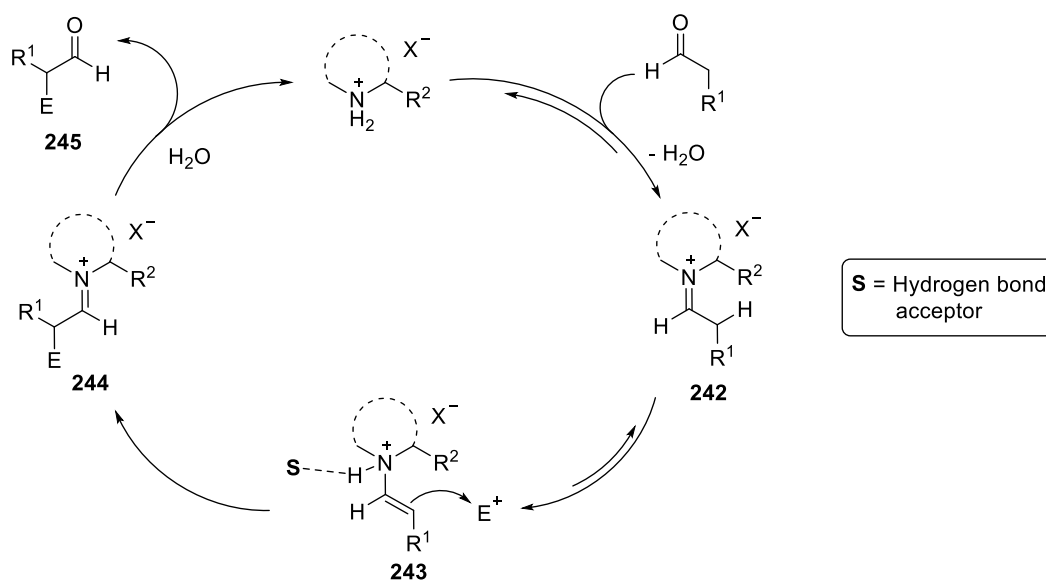
This strategy was later extended to improve the efficiency of transformations involving organo-enamine catalysis.²²² In this context, pyridine *N*-oxide was again identified as an extremely active catalytic additive with excellent reaction generality; accelerating the intramolecular Michael addition of **239**, α -fluorination of aldehyde **240** and the aldol reaction of dialdehyde **241** (Scheme 117) with great success.²²² Specifically, a 17.8, 8.0 and 17.4-fold rate enhancement relative to the background was observed for these transformations respectively when employing this additive at 20 mol% loading.²²² Notably, 8-methylquinoline *N*-oxide gave superior results for the intramolecular Michael addition of **239**, affording a 28.4-fold rate enhancement relative to the control experiment.²²²



Scheme 117. Effect of hydrogen bond acceptor additives on the rate of enamine catalysed transformations.²²²

For enamine catalysed transformations the associated catalytic cycle again involves two key stages (Scheme 118).^{222,225} During the first, enamine intermediate **243** is formed *via* dehydrative nucleophilic addition of the catalytic amine species to the carbonyl compound.^{222,225} Reaction of this enamine species (**243**) with an electrophile *via* either a substitution or addition pathway then generates an iminium ion **244**, which is hydrolysed to provide the product (**245**) with concomitant release of the amine catalyst (stage 2).^{222,225} Where the amine is weakly nucleophilic, Brønsted acids or amine salts are commonly employed to activate the carbonyl functionality of the substrate

in stage 1 and potentially also activate the electrophile and promote hydrolysis of the iminium in stage 2.²²² However, the acidic conditions leads to undesirable *N*-protonation of the enamine generating an enammonium cation **243**, which consequently reduces its nucleophilicity and makes stage 2 of the catalytic cycle rate determining.²²² In accordance with the gold catalysed system, proton abstraction is required to facilitate further reaction with an electrophile and it is thought that the role of the *N*-oxide is again to promote this by functioning as a hydrogen bond acceptor.^{221,222} Additionally, the *N*-oxide is believed to play a secondary role within this system; stabilising the enammonium cation *via* favourable hydrogen bonds and thus perturbing the equilibrium towards this species from the corresponding iminium tautomer **242**.²²² A similar stabilisation concept has been proposed to rationalise the catalysis observed within *N*-oxide promoted TPAP oxidations, as described in section 1.2.3.^{67,68}



Scheme 118. Proposed role of *N*-oxides and other hydrogen bond acceptors within enamine catalysed transformations.²²²

1.5 Conclusion to review of *N*-oxides

As a result of their Lewis basic nature, *N*-oxides have found application as both organocatalysts and neutral ligands within transition metal complexes; with recent research efforts being focussed on developing and applying chiral *N*-oxides within asymmetric transformations.^{1,2} Within coordination chemistry, *N*-oxides have been employed as chiral ligands to achieve stereochemical control and take advantage of their superior physical properties, such as their high solubility in water.^{1,2} Due to the intrinsic weakness of the N→O bond, *N*-oxides have additionally been utilised as stoichiometric oxidants for metals and organic substrates.¹ Whilst metal-free, *N*-oxide promoted reactions have primarily been reported within the arena of organosilicon chemistry, *N*-oxides have also been successfully applied as organocatalysts for the nucleophilic activation of phosphorous and carbon based substrates.^{2,7,93} Additionally, the potential of *N*-oxides to act as hydrogen bond catalysts represents an important and emerging area of interest.²¹⁸⁻²²²

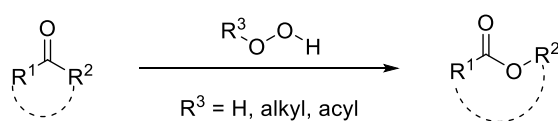
2 *N*-Oxides as hydrogen bond catalysts for the Baeyer-Villiger oxidation

2.1 Introduction

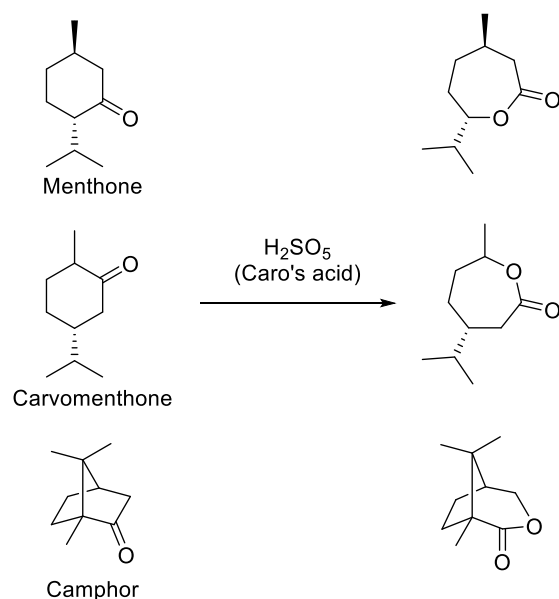
Although the application of *N*-oxides as hydrogen bond catalysts represents an emerging area of research, it is not yet well explored.²¹⁸⁻²²² Therefore, it was of interest to explore the potential of *N*-oxides as hydrogen bond catalysts within the Baeyer-Villiger oxidation, with the aim of extending the small portfolio of reactions that employ *N*-oxides in this role. The Baeyer-Villiger oxidation was identified as a suitable candidate for this, as the mechanism involves rate determining proton transfer and the transformation is of synthetic importance. A particular emphasis was placed on extending the methodology to the chemoselective oxidation of otherwise problematic α,β -unsaturated ketones.

2.1.1 Introduction to the Baeyer-Villiger oxidation

The Baeyer-Villiger oxidation represents an important methodology for converting acyclic and cyclic ketones into the corresponding esters and lactones respectively by their treatment with a stoichiometric peracid or peroxide species (Scheme 119).²²⁶⁻²³⁶ This type of oxidative transformation was first reported in 1899 by Baeyer and Villiger for a series of terpene-derived cyclic ketones, namely menthone, carvomenthone and camphor (Scheme 120).^{226,228,237-240} Within this pioneering study, peroxymonosulfuric acid (Caro's acid) was shown to successfully promote the previously unprecedented oxidation of such ketones into their lactone derivatives under solvent-free conditions.^{226,228,241} More recently, the Baeyer-Villiger oxidation has come to encompass the oxidation of aldehydes to the corresponding carboxylic acids or formates.²⁴¹⁻²⁴⁴

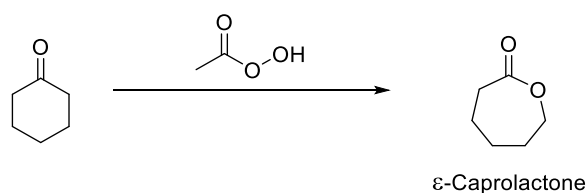


Scheme 119. The Baeyer-Villiger oxidation of ketones into the corresponding esters/lactones.²²⁶



Scheme 120. Peroxymonosulfuric acid (Caro's acid) mediated Baeyer-Villiger oxidation of cyclic ketones.^{226,228}

Since its discovery, the Baeyer-Villiger oxidation has become ubiquitous within the field of organic chemistry and has been applied to the synthesis of numerous natural products,²⁴⁵⁻²⁴⁸ antibiotics,^{249,250} steroids²⁵¹⁻²⁵³ and pheromones.²⁵⁴⁻²⁵⁷ Additionally, it has been utilised within the pharmaceutical industry for the multi-gram commercial synthesis of Travoprost; a prostaglandin analogue prescribed for glaucoma and ocular hypertension.^{258,259} Also within an industrial context, ϵ -caprolactone is produced annually on a >50,000 tonne scale principally from the Baeyer-Villiger oxidation of cyclohexanone with peracetic acid (Scheme 121).^{260,261} This ring-expanded lactone has found significant application as a monomer for the synthesis of biomedically relevant polymers and as a key intermediate in the manufacture of Nylon-6.²⁶¹⁻²⁶³



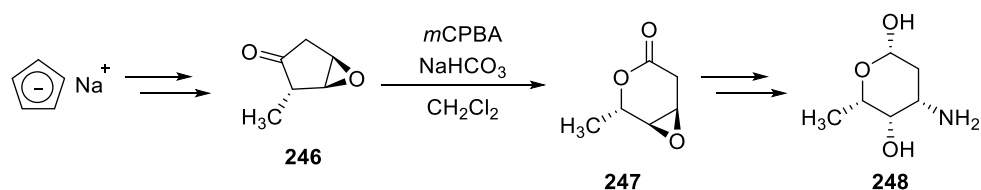
Scheme 121. Application of the Baeyer-Villiger oxidation to the industrial synthesis of ϵ -caprolactone.²⁶⁰

The success of the Baeyer-Villiger oxidation within such widespread applications can be attributed to its versatility; both with regards to the nature of the ketone and the oxidising agent, as well as the stereospecificity and highly predictable regioselectivity of the reaction.^{234,236-238,264-268} Structurally diverse ketones, from straight chain alkyl and aryl species to cyclic systems, have been found to be amenable to this methodology and a wide range of functional groups are tolerated.^{234,236-238,268} Whilst the presence of other readily oxidisable functionality (e.g. amines,

olefins) can result in the formation of multiple products, examples of chemoselective Baeyer-Villiger oxidations have been reported within the literature.^{234,238,242,269-272} Nevertheless, achieving the desired nucleophilic oxidation of the carbonyl over any competitive electrophilic oxidations can still present a challenge and reaction conditions may require adjusting for each individual substrate.^{241,270}

A diverse range of both inorganic and organic peracids as well as peroxide species have been documented as suitable oxidants for the Baeyer-Villiger reaction.^{238,242} From extensive studies it has been determined that the relative oxidising ability of some common reagents is as follows: trifluoroperacetic acid > monopermaleic acid > mono-*o*-perphthalic acid > 3,5-dinitroperbenzoic acid > *para*-nitroperbenzoic acid > *meta*-chloroperbenzoic acid (*m*CPBA) \approx performic acid > perbenzoic acid > peracetic acid >> hydrogen peroxide > *tert*-butylhydrogen peroxide.²³⁸ Whilst organic peracids are commonly prepared prior to use, they may also be formed *in situ* from the oxidation of the parent carboxylic acid with hydrogen peroxide.^{234,268}

As previously alluded to, the stereospecificity and high degree of regioselective control that the reaction affords are arguably two of the most important features.^{228,238} This is highlighted in the high yielding oxidation of unsymmetrical cyclic ketone **246** into lactone **247**, which is a key step in the asymmetric synthesis of amino sugar L-Daunosamine (**248**) reported by Grethe and co-workers (Scheme 122).²⁷³ Treatment of unsymmetrical cyclic ketone **246** with *m*CPBA was found to result in exclusive migration of the methyl substituted carbon producing a single regioisomeric product, lactone **247**.²⁷³ As is typically observed for Baeyer-Villiger oxidations, the stereochemistry of the migrating carbon was retained and a single stereoisomer was generated.^{234,273} These fundamental features of the Baeyer-Villiger oxidation can be rationalised by examining the reaction mechanism.

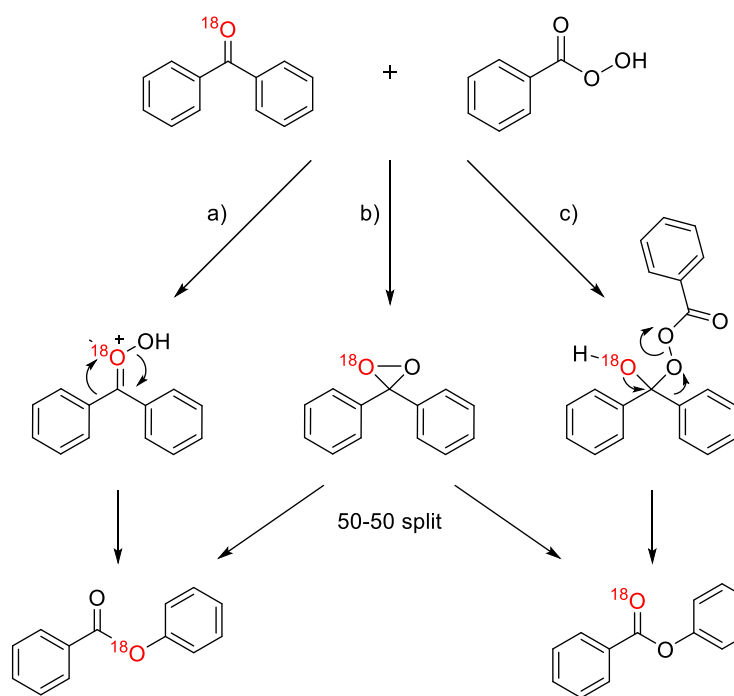


Scheme 122. Baeyer-Villiger oxidation as a key step in the synthesis of L-Daunosamine (**246**).²⁷³

2.1.2 Overview of the mechanism

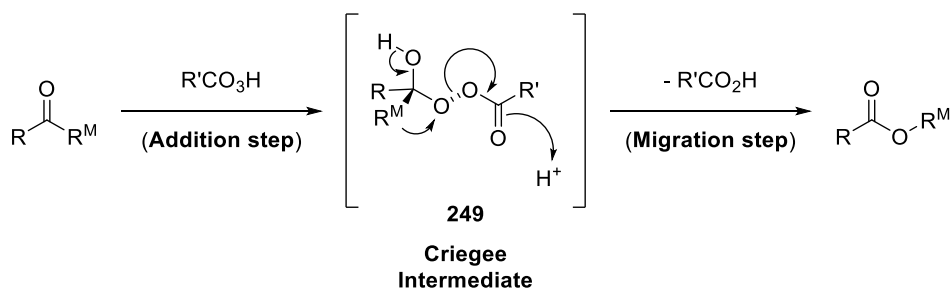
Owing to its complexity and the significance of the transformation effected, the mechanism of the Baeyer-Villiger oxidation has been the subject of multiple experimental and theoretical studies throughout the last century, which are still ongoing today.^{230,274-281} In 1950, three mechanistic pathways were considered by Doering and Speers as being consistent with their hypothesis that:

‘the migrating group is more electron deficient in the transition state’ than in the intermediate that precedes it.^{228,277} Subsequently, Doering and Dorfman devised an ^{18}O -labelling study to distinguish between these proposed mechanisms, which exploited the structural diversity of the intermediates formed and their unique modes of reactivity (Scheme 123).^{228,276} Utilising ^{18}O -labelled benzophenone, an oxidation proceeding *via* the Criegee intermediate would be expected to fully retain the ^{18}O -label within the carbonyl oxygen of the ester functionality (pathway c).^{228,276} Alternatively, this isotopic marker would be expected to be exclusively found within the phenolic oxygen for a mechanism involving a carbonyl oxide intermediate (pathway a).^{228,276} Finally, scrambling of the ^{18}O -label within the carbonyl moiety would occur if the ester was generated from a dioxirane intermediate, as the oxygen atoms are equivalent and a 50:50 mixture of the two labelled esters would be observed (pathway b).^{228,276} The position of the ^{18}O -label was unequivocally ascertained from mass spectrometry studies of the reduction products of phenyl benzoate: phenol and benzyl alcohol.^{228,276} It was reported that the ^{18}O -label was exclusively found within benzyl alcohol, which is derived from the carbonyl oxygen of the ester. Therefore, the authors concluded that the observed incorporation is only consistent with the mechanism postulated by Criegee.^{228,276} Due to its high reactivity and therefore transient nature, the Criegee intermediate has never been observed.²⁸² However, an analogous intermediate species, acetaldehyde monoperoxycarbonate, has been isolated at low temperatures for the addition of peracetic acid to acetaldehyde.^{282,283}



Scheme 123. ^{18}O labelling studies devised to determine the mechanism of the Baeyer-Villiger oxidation.²²⁸

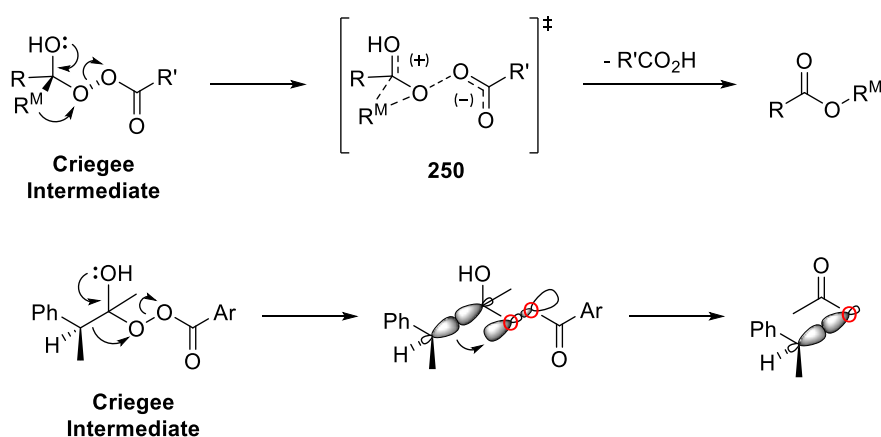
The development of this fundamental reaction has also been the subject of multiple reviews. In its most simplistic form the mechanism of the Baeyer-Villiger oxidation is considered to involve two discrete steps, as shown in Scheme 124.^{238,241,276} Initially, in the addition step, nucleophilic attack of the ketone carbonyl by the peracid generates tetrahedral species **249**, known as the ‘Criegee intermediate’.^{237,238,284} One of the substituents adjacent to the hemiketal carbon then migrates to the oxygen originating from the peracid, whilst the O-O bond is simultaneously cleaved; generating the desired ester with simultaneous release of the carboxylic acid moiety as the leaving group.^{237,238,284} This is typically referred to as the ‘migration step’.^{237,284}



Scheme 124. Mechanism for the Baeyer-Villiger oxidation.^{238,276}

Rearrangement of the Criegee intermediate in the absence of a catalyst has been shown from various studies to proceed *via* transition state **250**, for which migration occurs in a concerted rather than stepwise manner (Scheme 125).^{242,282,285-289} As demonstrated in Scheme 125, the migrating

group retains its tetrahedral geometry and moves with its bonding electrons in an sp^3 hybridised orbital to the adjacent σ^* orbital of the O-O bond.^{70,287} Thus, bond formation occurs on the same face of the migrating group, with the stereochemistry remaining unchanged, which accounts for the observed stereospecificity of the Baeyer-Villiger oxidation.^{70,238,287} Examination of the charge distribution in the transition state for migration has determined that the ester fragment exhibits a partial positive charge, whilst there is a partial negative charge residing on the departing acid fragment.^{227,232,280,290-292} Therefore, species that are best able to stabilise the developing negative charge, such as acids functionalised with electron-withdrawing groups, are superior leaving groups.^{234,238,272}



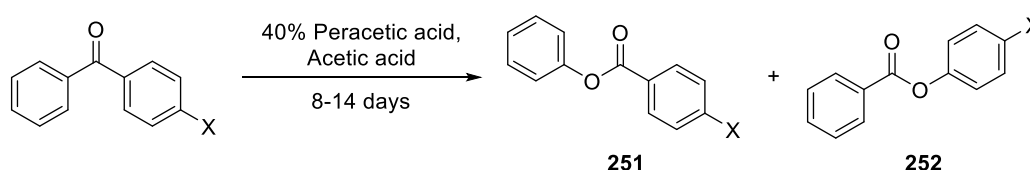
Scheme 125. Charge distribution and orbital interactions in the transition state for the migration step.⁷⁰

Intriguingly, the relative oxidising ability of an organic peracid, the reactivity series for which was given previously, is inversely correlated with its nucleophilicity and largely parallels the stability of the carboxylate leaving group.^{234,238,241,272,279} For instance, trifluoroperacetic acid has been found to be the most reactive peracid (*cf.* peracetic acid) despite being a poor nucleophile.^{238,268,281} One rationale that has been proposed to account for this increased reactivity, is the more rapid cleavage of the O-O bond and departure of the leaving group due to the stabilising inductive effect of the CF_3 functionality.^{238,268,293,294} Within systems where the migration is the rate determining step, it may be anticipated that the lower the pK_a of the carboxylic acid leaving group, the faster the reaction.^{238,272,294}

As demonstrated in Scheme 125, during the concerted rearrangement the developing positive charge is spread throughout the three-membered ring system of the transition state of the ester fragment.^{70,279,292} For unsymmetrical ketones, the carbonyl substituent that migrates is typically the one that is best able to stabilise the partial positive charge.^{232,233,242,277,291,294} A seminal publication by Doering *et al.* first outlined this electronic argument, which was substantiated by the results of their study into the competitive migration for a series of unsymmetrically substituted

benzophenone derivatives (Table 3).^{228,277} From analysis of the product distributions, the authors were able to conclude that aromatics bearing charge-stabilising, electron-donating substituents migrated in preference to the electron neutral phenyl ring, whilst the presence of an electron-withdrawing group reduced the migratory aptitude of the aromatic relative to an unsubstituted phenyl ring.^{228,277} Based on these observed migratory aptitudes as well as the relative rates reported by Friess *et al.* for the perbenzoic acid oxidation of a series of electronically diverse substituted acetophenones, the following order of migratory ease has been postulated for substituted phenyl rings: $p\text{-OCH}_3 > p\text{-CH}_3 > \text{H} > p\text{-Cl} > p\text{-Br} > p\text{-NO}_2$.^{228,277,295} As this series demonstrates, the more electron-donating the aromatic functionality, the more capable the group is of supporting a positive charge and therefore the greater the migratory aptitude.^{277,295} However, it should be noted that reaction rates alone cannot be used in isolation to determine migratory aptitudes, as a change in the electronics of a substrate can also induce a change in the rate determining step of the reaction.^{227,228,232,241,244,268,281,292,296,297} Additionally, subtle changes in the structure and electronics of the ketone substituents are known to induce a change in product distribution.^{233,272}

Table 3. Product distributions for the peracetic acid oxidation of unsymmetrically substituted benzophenone derivatives.^{228,277}

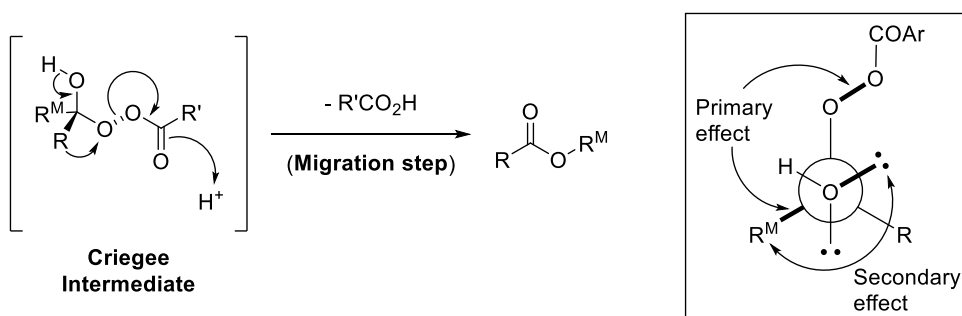


Entry	<i>para</i> substituent (X)	Product distribution 251/252	Yield (%)	Yield recovered ketone (%)
1	CH ₃ O	0:100	86	0
2	CH ₃	0:100	47	39
3	H	-	45	46
4	Cl	91:9	22	74
5	Br	- ^a	3	94
6	NO ₂	100:0	29	0

^aPreferential phenyl group migration observed but ratio not determined due to low conversion. Opposite regioselectivity observed in the presence of sulfuric acid.

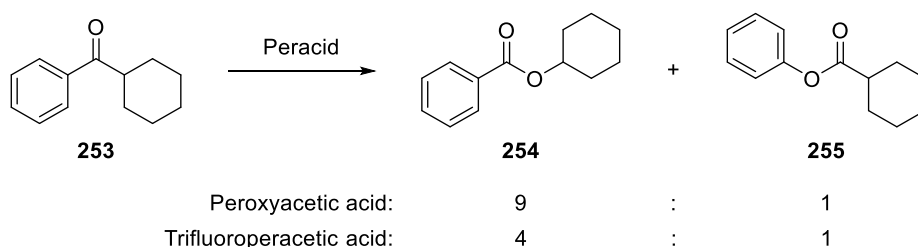
Based on the results of numerous studies, the approximate sequence of migratory aptitude has been determined as: tertiary alkyl > cyclohexyl > secondary alkyl > benzyl > phenyl > primary alkyl > cyclopentyl, cyclopropyl > methyl.²²⁸ As previously detailed, it is this predictable regiochemistry that contributes to the synthetic appeal of the Baeyer-Villiger oxidation.^{234,237,238} As the methyl group has such a low ability to stabilise the positive charge and therefore rarely migrates, methyl ketones are frequently utilised as precursors to acetate esters.^{228,242,275}

In addition to electronic considerations, steric and conformational factors are also important in determining which group will migrate; with the latter particularly relevant for bicyclic substrates due to their constrained geometry.^{238,294,298,299} Rearrangement of the Criegee intermediate can only occur if the following stereoelectronic requirements are met: 1) the migrating group (R^M) must be aligned antiperiplanar to the O-O bond, as this orientation ensures the most effective overlap of the σ_{C-R^M} orbital and the σ^*_{O-O} orbital (primary stereoelectronic effect) and 2) the migrating group (R^M) must be aligned antiperiplanar to one of the lone pairs on the oxygen of the hydroxyl group (secondary stereoelectronic effect) (Scheme 126).^{227,236,268,278,298,300-304}



Scheme 126. Newman projection detailing the stereoelectronic requirements of the Baeyer-Villiger oxidation.²⁷⁸

Interestingly, the identity of the peracid has been found to influence the regioselectivity and product distribution, as evidenced by the work of Hawthorne and co-workers into the oxidation of cyclohexyl phenyl ketone (**253**) (Scheme 127).^{228,244,294} Whilst migration of the cyclohexyl substituent is favoured in both cases, the oxidation of **253** performed with peroxyacetic acid provided a selectivity of 9:1 in favour of ester **254** compared with only a 4:1 ratio (**254:255**) with the more reactive trifluoroperacetic acid.^{228,294} It has been noted that the lower the oxidising ability of the peracid:acid combination, the more selective the oxidation.^{242,294,305} Although the reaction conditions can alter the regiochemical outcome, this effect is primarily observed for ketones substituted with groups of similar migratory aptitude.²⁹⁴



Scheme 127. Effect of the peracid identity on the regioselectivity afforded within the oxidation of cyclohexyl phenyl ketone.^{228,294}

2.1.3 Catalytic strategies and modes of activation

The specific role of a catalyst within the Baeyer-Villiger oxidation is dependent upon which step exhibits the highest activation energy, although this is often undetermined.²⁶⁸ However, the energy barrier to both steps is often within the same order of magnitude and similar catalytic strategies can be applied to enhance the rate of both the addition and migration.^{241,268} Therefore, the rate determining step does not necessarily need to be known. In some cases the catalyst may even interact with both transition states, lowering the energy barrier for both.^{241,268} It may be envisioned that the Baeyer-Villiger oxidation can be catalysed *via* any of the modes of activation outlined in Figure 22, as detailed in a review by ten Brink *et al.*²⁶⁸

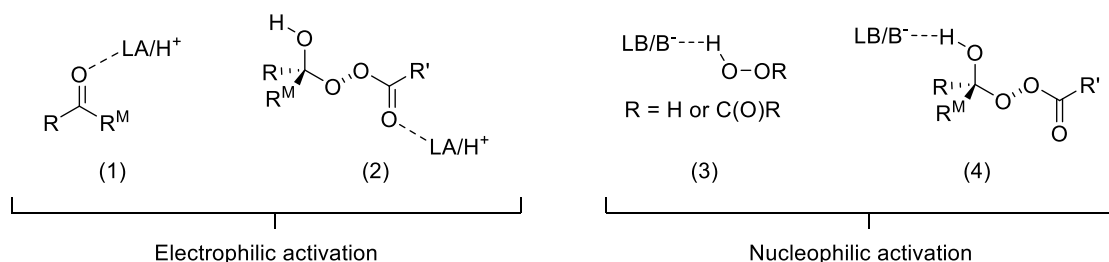
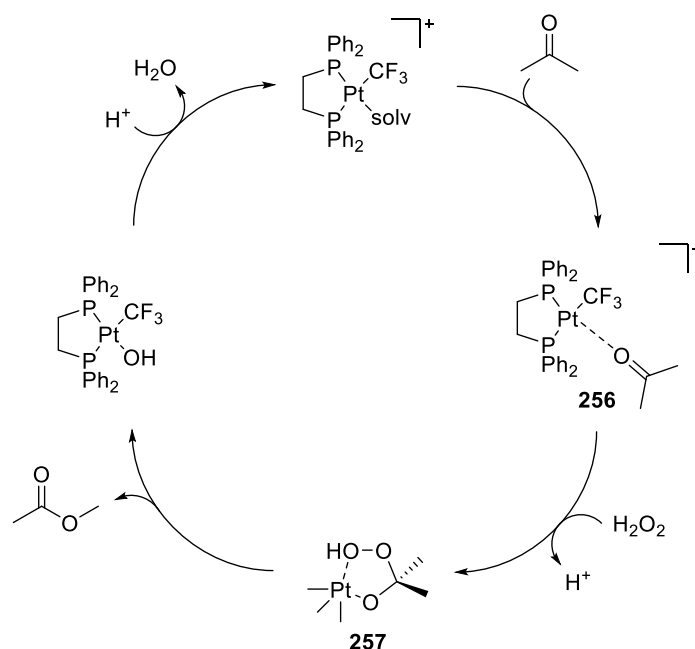


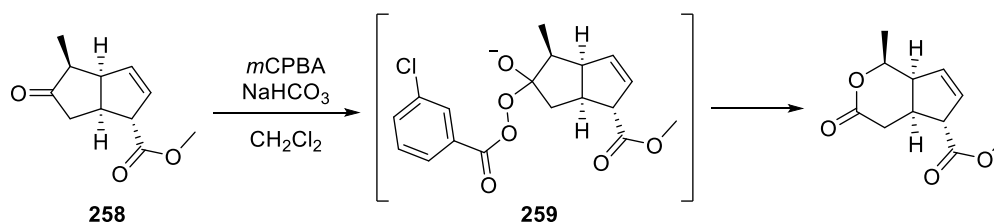
Figure 22. Modes of activation employed to catalyse the Baeyer-Villiger oxidation.²⁶⁸

Commonly, catalysts are employed for the electrophilic activation of the ketone and/or Criegee intermediate (modes (1) and (2), Figure 22).^{234,268} For instance, Strukel and co-workers have suggested that in the Pt(II) catalysed oxidation of cyclic ketones with H₂O₂ both of these modes of activation are in operation (Scheme 128).^{268,306} Specifically, the electrophilicity of the ketone carbonyl is enhanced by coordination to the cationic platinum complex (**256**), which facilitates attack by the unbound hydrogen peroxide.^{234,238,268,306} Additionally, migration is promoted by coordination of the normally poor hydroxyl leaving group to the platinum centre (**257**).^{234,238,268,306} Quasi-peroxymetallacyclic intermediate **257** is reminiscent of the Criegee intermediate, with H⁺ essentially substituted for Pt⁺.^{234,238,306} This methodology represents one of the earliest examples of a transition metal catalysed Baeyer-Villiger oxidation.²³⁴ Lewis acidic homogeneous and heterogeneous catalysts,^{234,238,241,268} Brønsted acids^{268,281} and biocatalysts^{237,268,307} have all been successfully used in the context of electrophilic activation.

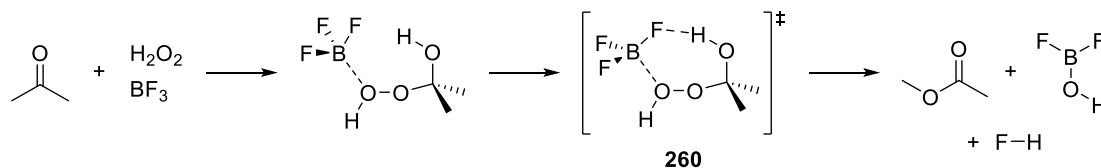


Scheme 128. Electrophilic activation within the Pt(II) catalysed oxidation of cyclic ketones with H_2O_2 .^{268,306}

Alternatively, catalysis may be achieved *via* nucleophilic activation of the oxidising agent or Criegee intermediate (modes (3) and (4), Figure 22).²⁶⁸ With respect to the oxidising agent, the nucleophilicity can be enhanced by deprotonation prior to or during the addition step.²⁶⁸ Specific to the use of hydrogen peroxide, the formation of a metal hydroperoxo species ($\text{M}-\text{OOH}$, $\text{M} = \text{Pd}$, Pt , Ti) has been reported to successfully enhance the peroxide nucleophilicity and thus promote the desired reaction.^{234,238,241,268} As rearrangement is initiated by a flow of electron density from the lone pair of the hydroxyl oxygen in the Criegee intermediate, abstraction of the hydroxyl proton promotes reformation of the carbonyl bond and accelerates the rate of the second step.^{268,272,282} This mode of catalysis has been postulated for the heterogeneous sodium bicarbonate catalysed oxidation of cyclic ketone **258** with *m*CPBA in DCM reported by Whitesell *et al.* (Scheme 129) and more recently for the oxidation of acetone with H_2O_2 catalysed by BF_3 developed by Brinck and co-workers (Scheme 130).^{228,268,308,309} In the former, the sodium bicarbonate is thought to be acting as a Brønsted base to generate an anionic Criegee intermediate (**259**), whilst the BF_3 facilitates the rearrangement *via* proton transfer of the hydroxyl proton to the electronegative fluorine in the transition state (**260**) forming HF as a by-product.^{228,268,308,309} Both Lewis basic heterogeneous and homogenous catalysts,^{234,238,241,268} Brønsted bases,³⁰⁹ organocatalysts^{310,311} and biocatalysts^{237,268,307,312} have all been implemented for the nucleophilic activation approach.



Scheme 129. Nucleophilic activation within the heterogeneous sodium bicarbonate catalysed oxidation of cyclic ketone **258**.³⁰⁹



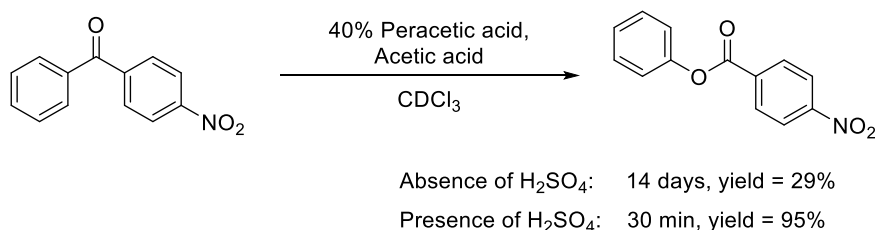
Scheme 130. Nucleophilic activation within the BF₃ catalysed Baeyer-Villiger oxidation of acetone with H₂O₂.³⁰⁸

The development of suitable catalysts for the Baeyer-Villiger oxidation has been the topic of several comprehensive reviews.^{234,237,238,241,268} Much recent work has been focussed on utilising greener oxidants, such as O₂ and in particular hydrogen peroxide, as the sole by-product is water rather than an equivalent of carboxylic acid.^{238,241,268} This additionally simplifies the work-up procedure and prevents any undesirable acid-catalysed side reactions.^{238,268} However, due to the nucleophilic activation required and the poor leaving group subsequently generated (OH⁻), hydrogen peroxide is inherently less reactive than traditionally used peracids and therefore typically requires a suitable catalyst, as highlighted in the examples above.^{241,268,313}

2.1.4 Brønsted acid catalysed Baeyer-Villiger oxidations

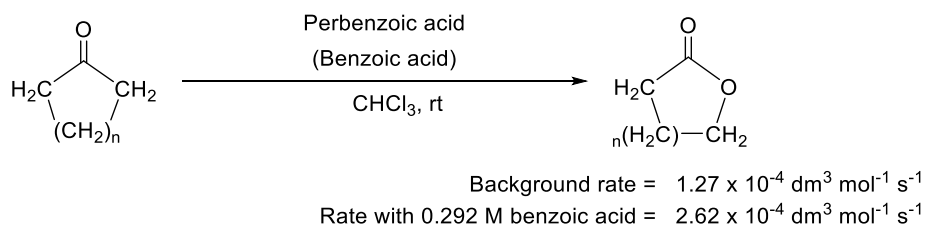
It has long been known that Brønsted acids catalyse the Baeyer-Villiger oxidation. For instance, in 1950 Doering and Speers observed a significant acceleration in the rate of peracetic acid oxidations of *p*-substituted benzophenones when the reaction was performed using 13-vol% concentrated sulfuric acid as a co-solvent, as opposed to acetic acid alone (Scheme 131).^{228,277,281} In many cases, reaction times of several days were reduced to just 30 minutes and the yields were also improved.^{228,277,281} To date, several strong Brønsted acids have been reported to successfully catalyse the Baeyer-Villiger oxidation, including sulfuric acid,²⁷⁷ phosphoric acid derivatives,^{314,315} perchloric acid,^{242,316} Nafion-H,³¹⁷ *p*-toluenesulfonic acid^{242,318-320} and trifluoroacetic acid.^{293,294} A stepwise and ionic process involving specific acid catalysis has been identified for such strong mineral acids and the activation energy barrier to both steps may be considerably reduced.^{277,281,321} However, these systems often suffer from undesired acid-catalysed

rearrangements and transesterification, particularly where the products are acid sensitive, which can limit the use of such catalysts.^{228,238,293,294,322}



Scheme 131. Catalytic effect of sulfuric acid within the oxidation of substituted benzophenones with peracetic acid.²⁷⁷

More interestingly, within peracid oxidations general acid catalysis has been observed in the presence of weak acids, such as carboxylic acids.^{228,294,295,297,323-325} For example, in 1949 Friess reported that the oxidation of cyclic ketones with perbenzoic acid exhibited second order reaction kinetics and was acid catalysed; with the rate dependent upon the concentration of benzoic acid present (Scheme 132).^{323,325} Due to their inherent instability and the preparative methods used, organic peracids are typically accompanied by varying quantities of the parent carboxylic acid.^{228,323,326} Therefore, this type of oxidant is essentially prepared in combination with a suitable catalyst for the Baeyer-Villiger oxidation.^{281,323} As an equivalent of carboxylic acid is formed as a by-product, Baeyer-Villiger oxidations performed with peracids are typically autocatalytic.^{233,281,323} Evidence for this was also provided by Friess, who observed a gradual increase in the rate constant as the perbenzoic oxidation proceeded, which is indicative of an increase in concentration of the catalyst as the reaction progresses.³²³ Hawthorne and Emmons later reported this phenomenon for oxidations performed using trifluoroperacetic acid in a 10:1 (volume) acetonitrile:1,2-dichloroethane mixture.^{228,325} In this instance, the relatively strong carboxylic acid, trifluoroacetic acid, was proposed to be catalysing the reaction.³²⁵ Crucially, as noted by Meunier *et al.*, the kinetics of the Baeyer-Villiger oxidation cannot be compared across different batches of peracid or where an acidic species is employed as an additive/solvent, unless the identity and exact concentration of acid is known.^{228,325}

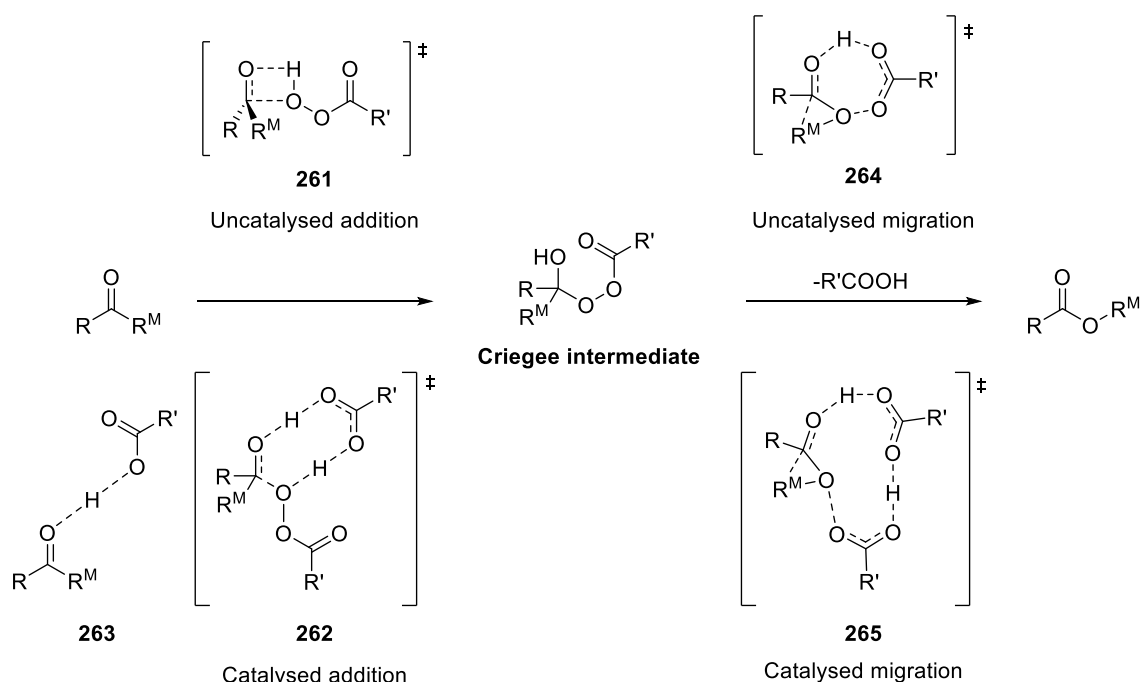


Scheme 132. Examination of the catalytic effect of benzoic acid within the perbenzoic acid mediated oxidation of cyclic ketones.^{323,325}

As previously detailed, the relative reactivity of a peracid is not determined by its nucleophilicity; with trifluoroperacetic acid displaying uncharacteristically strong oxidising potential as a nucleophilic oxidant.²⁶⁸ Whilst the trend in oxidising ability can be explained by considering the stability of the leaving group, the reactivity series also parallels the strength of the accompanying carboxylic acid.^{232,234,268,297,326} The stronger the parent carboxylic acid, the more effective the acid catalysis and the greater the oxidising ability of that peracid system.^{232,291,296} Helping to substantiate this argument, Rassat and Ourisson demonstrated that trifluoroperacetic acid oxidations performed in a phosphate buffered system resulted in diminished reaction rates.^{228,268} For this particular system, acid catalysis appears to be more important in determining the reaction rate than the leaving group ability or nucleophilicity of the peracid.^{232,291}

2.1.5 Importance of proton transfer processes within the oxidation mechanism

In recent years, several significant theoretical investigations have been conducted to determine the exact role of the carboxylic acid catalyst and also which step of the reaction is catalysed.^{227,230-233,243,244,280,281,290,292,296,321,326,327} It is generally accepted that reactions performed in non-polar solvents and in the presence of these weak acids will proceed *via* the concerted, non-ionic mechanism shown in Scheme 133.^{230,232,280,281,291,321,327} In instances where the carboxylic acid is involved in the transition state, it essentially functions as a proton shuttle; accepting a proton onto the carbonyl functionality, whilst simultaneously donating its acidic proton.^{230,233,280,281,292,296}



Scheme 133. Concerted, non-ionic mechanism proposed for the Baeyer-Villiger oxidation in non-polar solvents, with both the uncatalysed and acid catalysed transition states shown.^{231,327}

For all systems explored, the first step has been found to be acid catalysed, whilst the second step may or may not involve acid catalysis depending on the specifics of the system.^{232,280,281,291} Focussing on the initial step, the activation energy of the uncatalysed addition, which proceeds *via* the 4-membered cyclic system **261**, was calculated to be prohibitively high in all instances and is therefore proposed to occur very slowly, if at all.^{233,280,281,292,296} As the addition is energetically disfavoured in the absence of a catalyst and reasonable quantities of carboxylic acid are always present in oxidations performed using peracids, it has been suggested that experimentally only the acid promoted addition pathway will be in operation.^{232,280,291,326} To date, **262** is the lowest energy transition state that has been identified for a concerted, acid-catalysed addition in non-polar solvents (Scheme 133), which was proposed by Alvarez-Idaboy and co-workers from their studies into the acetic acid catalysed oxidation of acetone with peracetic acid.²³⁰ For some systems it has been reported that a complex initially forms between the ketone and carboxylic acid (**263**), which then goes on to react with the relevant peracid *via* transition state **262** (Scheme 133).^{232,280,281,291,326,327} On the basis of the calculated Gibbs free energy barriers, it has been suggested that a stronger carboxylic acid achieves a greater degree of proton transfer and therefore activation within the addition step.^{232,244,291,296,321,326} Additionally, Hu *et al.* ascertained that it is not energetically feasible for a molecule of the peracid, *m*CPBA, to adopt the role of the proton transfer catalyst.²⁹⁶

Introduction of a carboxylic acid has been found to provide a more modest reduction in the enthalpy associated with migration, which may be outweighed by the entropy loss.^{233,280,281,291,326} As a result, within the majority of computationally studied systems an uncatalysed migration proceeding *via* the unimolecular cyclic transition state **264** was found to be slightly lower in energy (Scheme 133).^{227,232,280,281,326,327} In cases where the carboxylic acid does catalyse the migration (**265**), it participates in the transition state by operating as a proton relay catalyst in the same manner as that observed for the addition step.^{233,280,281} Regardless of whether the migration is acid catalysed, the rate of migration is influenced by the identity of the peracid:carboxylic acid combination, as this directly affects the leaving group ability.^{232,291}

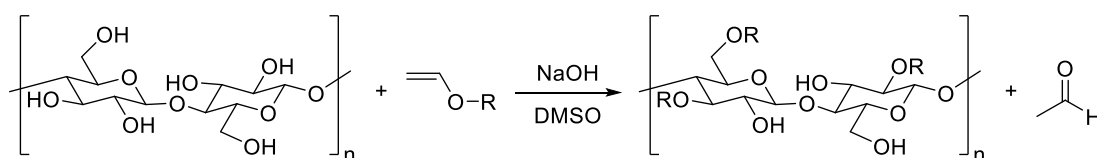
Organic acids therefore play an integral role within peracid mediated Baeyer-Villiger oxidations, as they possess the potential to function as hydrogen bond catalysts.^{230,232,233,280,281,292,296} Whilst the addition step is rate determining for reactions performed without an accompanying catalyst, in the presence of a carboxylic acid the degree of stabilisation achieved for this first transition state is far greater.^{232,233,244,280,281,290,296} Therefore, the rate determining step in the presence of acid may be either the addition or migration step.^{227,230,232,280,281,291,296} Additionally, as the two transition states are influenced to different extents by changes to the reaction system, small modifications to the electronics, sterics or substitution pattern of the carbonyl compound or minor alterations to

the reaction conditions (peracid:acid combination, catalyst, solvent, acidity of the reaction medium) may be enough to alter the kinetically significant step.^{227,228,232,241,244,268,281,292,296,297} Evidently, predicting the rate-determining step for the Baeyer-Villiger oxidation remains a challenge.

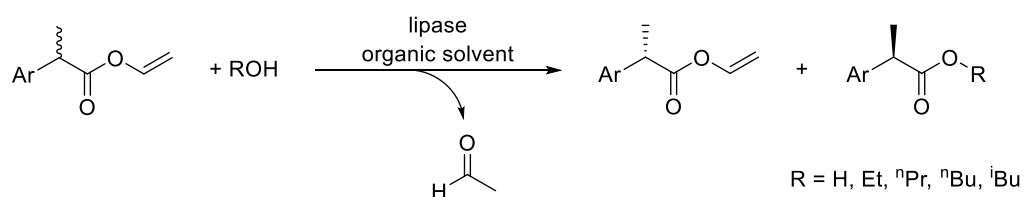
2.1.6 Baeyer-Villiger oxidation of α,β -unsaturated ketones

There are isolated reports within the literature of the Baeyer-Villiger oxidation being applied to α,β -unsaturated ketones; many of which have been collated in an extensive review by Krow.²⁴² This substrate class is of particular interest due to the synthetic utility of the obtained vinyl esters/enol lactones, which are versatile building blocks for organic synthesis.^{328,329} In this regard, industrially relevant cellulose esters can be synthesized from the transesterification of naturally abundant, renewable cellulose with short, aliphatic straight chain vinyl esters (Scheme 134).³³⁰ Vinyl esters are also of interest as potential monomers for the synthesis of more complex derivatives of polyvinyl acetate (PVA).^{328,331} Additionally, optically pure esters and carboxylic acids, such as profens, have been prepared from activated, racemic vinyl ester species *via* resolution involving irreversible transesterification or hydrolysis respectively (Scheme 135).³³²⁻

336



Scheme 134. Transesterification of naturally abundant, renewable cellulose with short, aliphatic straight chain vinyl esters.³³⁰



Scheme 135. Application of vinyl esters to the preparation of optically pure carboxylic acids.³³²

Vinyl esters are also important in their own right, as this functional motif is found within many natural products, which have been shown to exhibit antibacterial,³³⁷ antimicrobial,³³⁸ anti-cancer³³⁷⁻³⁴⁰ and fungicidal^{341,342} properties (Figure 23).

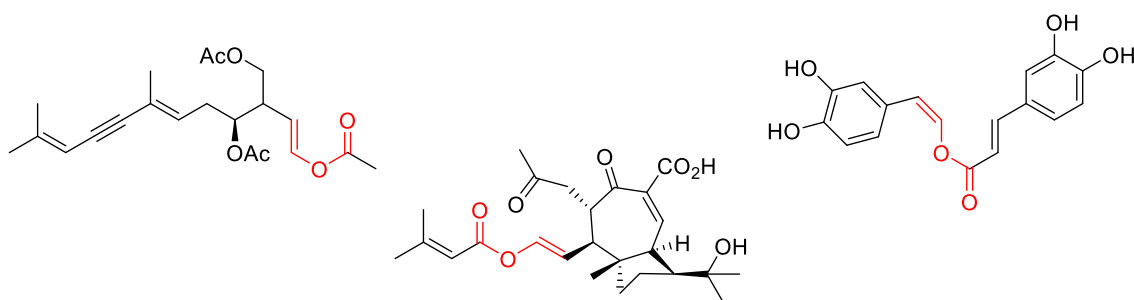
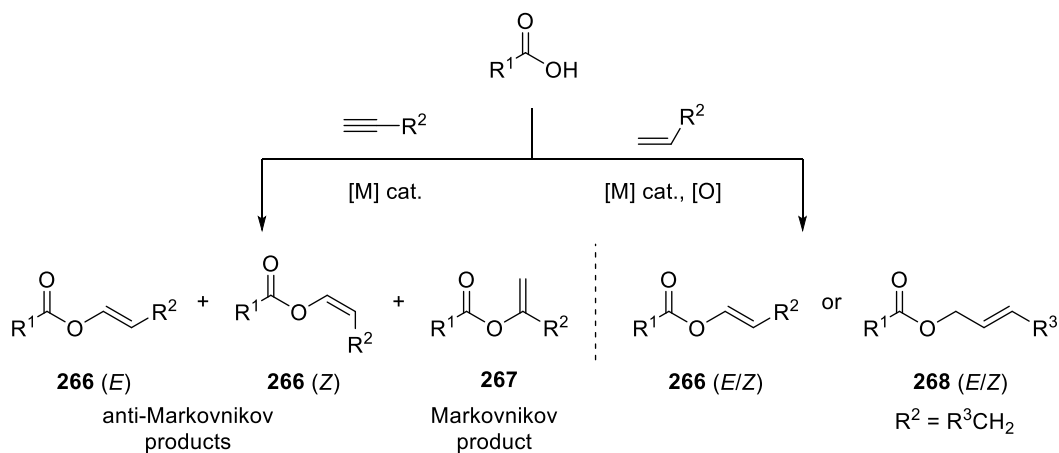


Figure 23. Natural products containing a vinyl ester functionality.^{337,339,341,342}

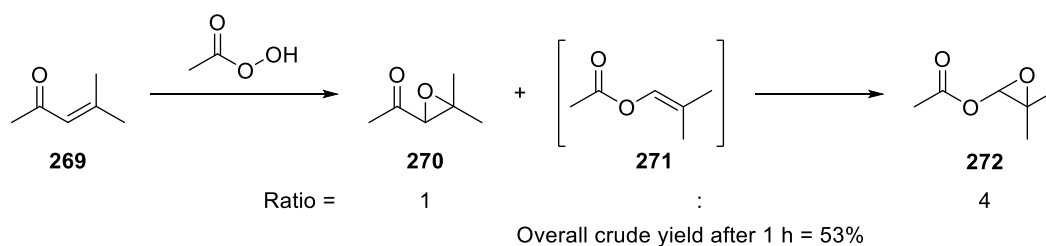
This class of compound was traditionally prepared *via* transition metal-mediated anti-Markovnikov addition of carboxylic acids to terminal alkynes or *via* oxidative/dehydrogenative coupling of alkenes with carboxylic acids (Scheme 136).^{328,329,343-345} Although these methods exhibit high atom economy and employ easily accessible carboxylic acids, they frequently suffer from relatively poor *E/Z* stereoselectivity, with the vinyl ester (**266**) generated as an undesirable mixture of both isomers.^{328,329,343-345} Additionally, it can be difficult to obtain high regioselectivity within the cross coupling of alkynes with carboxylic acids, resulting in the formation of both the anti-Markovnikov (**266**) and Markovnikov (**267**) adducts.^{329,344,345} Furthermore, substrates containing an alkene moiety adjacent to an sp^3 hybridised carbon have been reported to undergo an allylic rearrangement to produce the corresponding allylic ester **268** in preference to the vinyl ester species **266**.^{329,343,346,347}



Scheme 136. Transition metal mediated synthesis of vinyl esters from carboxylic acids.^{329,344}

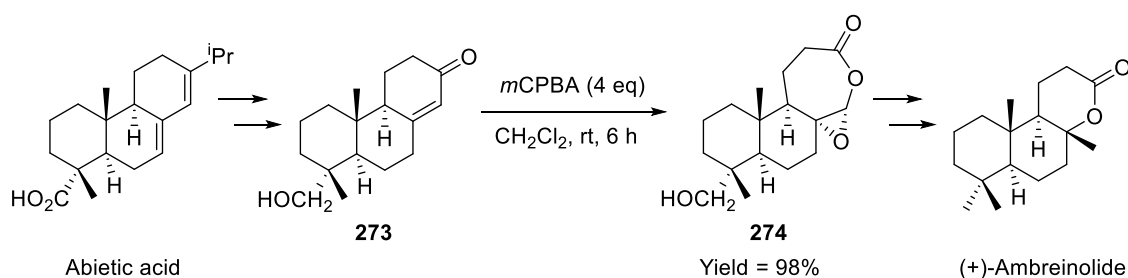
The Baeyer-Villiger oxidation would therefore provide an alternative, metal-free and stereospecific approach for the synthesis of vinyl esters from easily prepared α,β -unsaturated ketones.^{328,329} However, with the exception of two oxidative procedures reported during the course of this work,^{328,329} current methodologies have several limitations. For instance, the Baeyer-Villiger oxidation of α,β -unsaturated ketones commonly suffers from reduced yields due to competing epoxidation reactions.^{242,348}

A particularly extreme example of this was reported by Payne and Williams for the oxidation of 4-methyl-3-pentene-2-one **269** with peroxyacetic acid (Scheme 137).^{242,349} Instead of the expected vinyl ester **271**, the authors reported that epoxides **270** and **272** were afforded in a 1:4 ratio and a combined crude yield of 53% based on peracid consumption.^{242,349} As epoxy ketone **270** gave negligible conversion (<5%) to epoxy ester **272** when subjected to the oxidative reaction conditions, it was proposed that epoxy ester **272** was formed from the oxidation of vinyl ester **271**, which was generated as an intermediate during the reaction.^{242,349} It was concluded that the rate of peracid epoxidation was much higher for the vinyl ester than the parent α,β -unsaturated ketone.^{242,349}

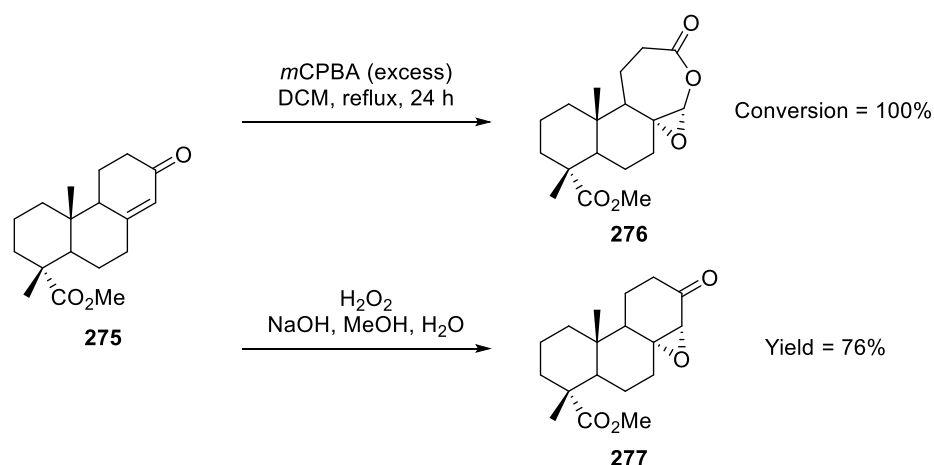


Scheme 137. Competing epoxidation reactions.^{242,349}

Typically, the double bond of a vinyl ester is more electron rich and possesses more nucleophilic character than the double bond of an α,β -unsaturated ketone and is therefore more susceptible to oxidation by a peracid, which acts as an electrophilic oxidant in this instance.³⁵⁰ Consequently, larger quantities of the epoxy ester relative to epoxy ketone are often observed for peracid oxidations.^{242,349,351} This is clearly demonstrated in the oxidation of α,β -unsaturated ketone **273** with *m*CPBA in dichloromethane performed by Abad and co-workers as an important step in the preparation of (+)-Ambreinolide from *l*-abietic acid (Scheme 138).^{242,352} In the presence of a large excess of *m*CPBA, epoxy lactone **274** was generated in essentially quantitative yield (>95% purity, as determined by ¹H NMR).³⁵² Similarly, Pelletier *et al.* reported that, upon refluxing α,β -unsaturated ketone **275** for 24 hours with an excess of *m*CPBA, epoxy lactone **276** could be generated as the exclusive product (Scheme 139).^{351,353} Irrespective of peracid concentration, epoxy ketone **277** was not observed.³⁵³ Alternatively, oxidations performed with alkaline hydrogen peroxide, which is classified as a nucleophilic oxidant, are typically found to provide high yields of the epoxy ketone.³⁵³⁻³⁵⁵ Within the same study, epoxy ketone **277** was synthesized in 76% yield from **275** when using hydrogen peroxide in aqueous methanolic sodium hydroxide as the oxidant.³⁵³

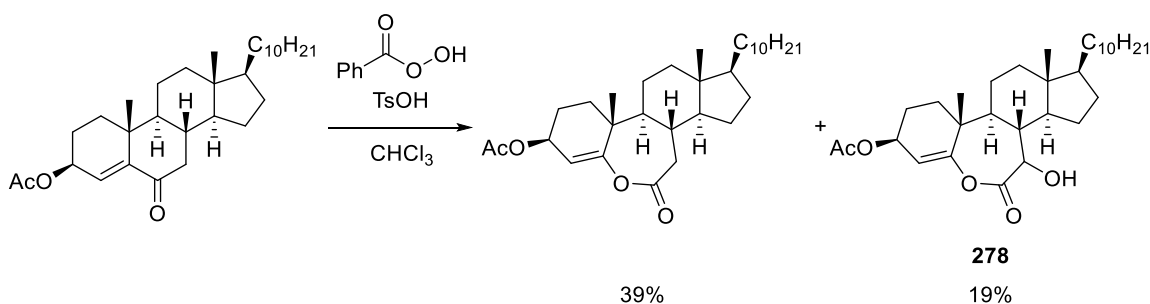


Scheme 138. Epoxy ester formation as a key synthetic step in the synthesis of (+)-Ambreinolide.³⁵²



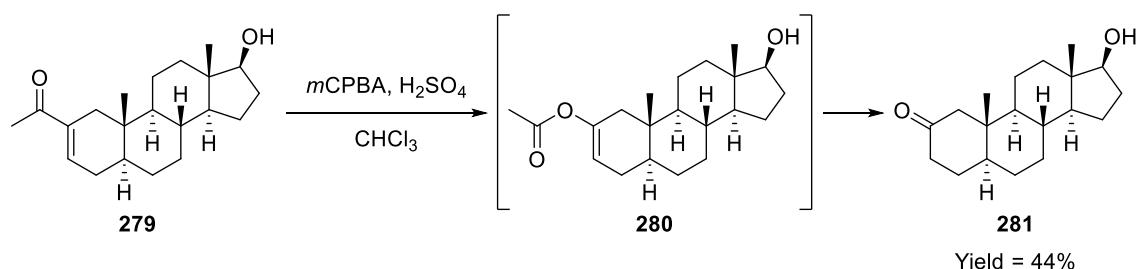
Scheme 139. Effect of the oxidant on product selectivity for the reaction of α,β -unsaturated ketone 275.³⁵¹

α -Hydroxy enol lactones, such as **278**, may also be formed from competing epoxidation reactions and have been reported for a range of cyclic enones, such as steroidal-4-en-6-ones, for which the carbonyl is adjacent to a saturated methylene unit.^{242,356,357} In this instance, epoxidation of the enol tautomer of the ketone occurs initially. Intramolecular ring opening of the resultant epoxide and subsequent oxidation of the *in situ* generated α -hydroxy ketone then affords the observed α -hydroxy enol lactone by-product (Scheme 140).^{242,356,357}



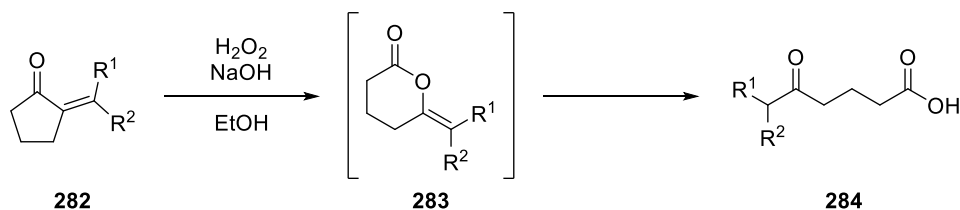
Scheme 140. Formation of α -hydroxy enol lactone **278**.^{242,356}

Additionally, it has been reported that for certain substrate classes, further undesired side reactions and therefore degradation can occur when applying current methodologies.^{242,358} This is particularly true where the product is sensitive to acid or base. From several publications it has been identified that vinyl esters and epoxy esters may be susceptible to irreversible hydrolysis.²⁴² For instance, 2-ketosteroid **281** was isolated in 44% yield from the reaction of cyclohexenyl ketone **279** with *m*CPBA, which formed from hydrolysis of the intermediate enol acetate **280** (Scheme 141).^{242,359}



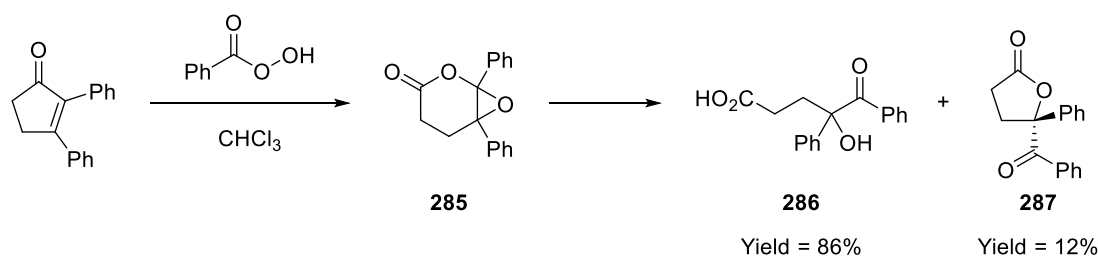
Scheme 141. Irreversible hydrolysis of enol acetate intermediate **280** to 2-ketosteroid **281**.²⁴²

Similarly, Ijima *et al.* found that exocyclic enol lactones **283**, which form under basic conditions by the action of hydrogen peroxide on the corresponding exocyclic α,β -unsaturated ketones **282**, hydrolysed under the reaction conditions to give ring opened, straight chain keto acid species **284** (Scheme 142).^{242,360}



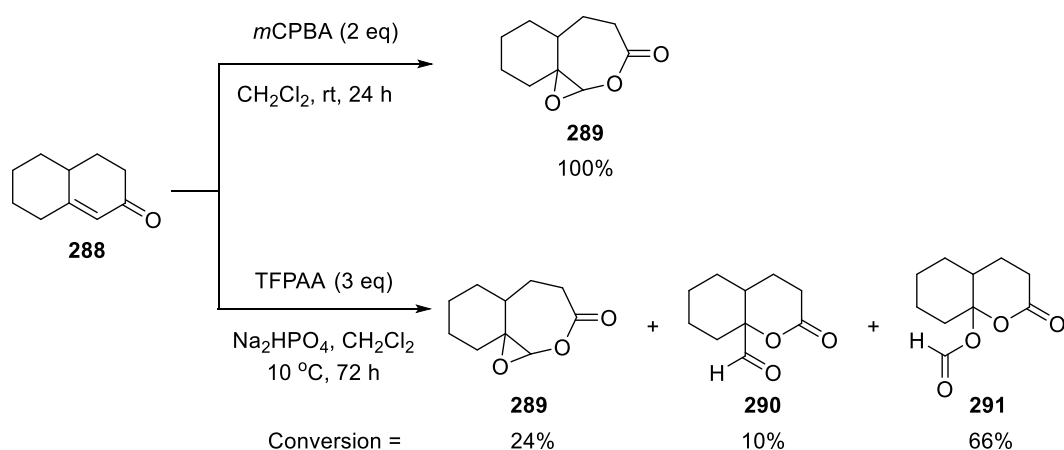
Scheme 142. Hydrolysis of intermediate exocyclic enol lactones (**283**) to give straight chain keto acids (**284**).²⁴²

Analogous hydrolysis of epoxy esters (**285**) generates straight chain acids containing an α -hydroxyketone moiety (**286**), which may participate in subsequent intramolecular esterification to generate ring contracted lactones (**287**).²⁴² For example, Yokoyama and Izui reported that epoxy esters derived from cycloalkenone type substrates (**285**) undergo ring opening ester hydrolysis to generate acid **286**, with subsequent re-esterification forming lactone **287** (Scheme 143).^{242,361}



Scheme 143. Undesired hydrolysis of epoxyester **285** and subsequent intramolecular esterification.²⁴²

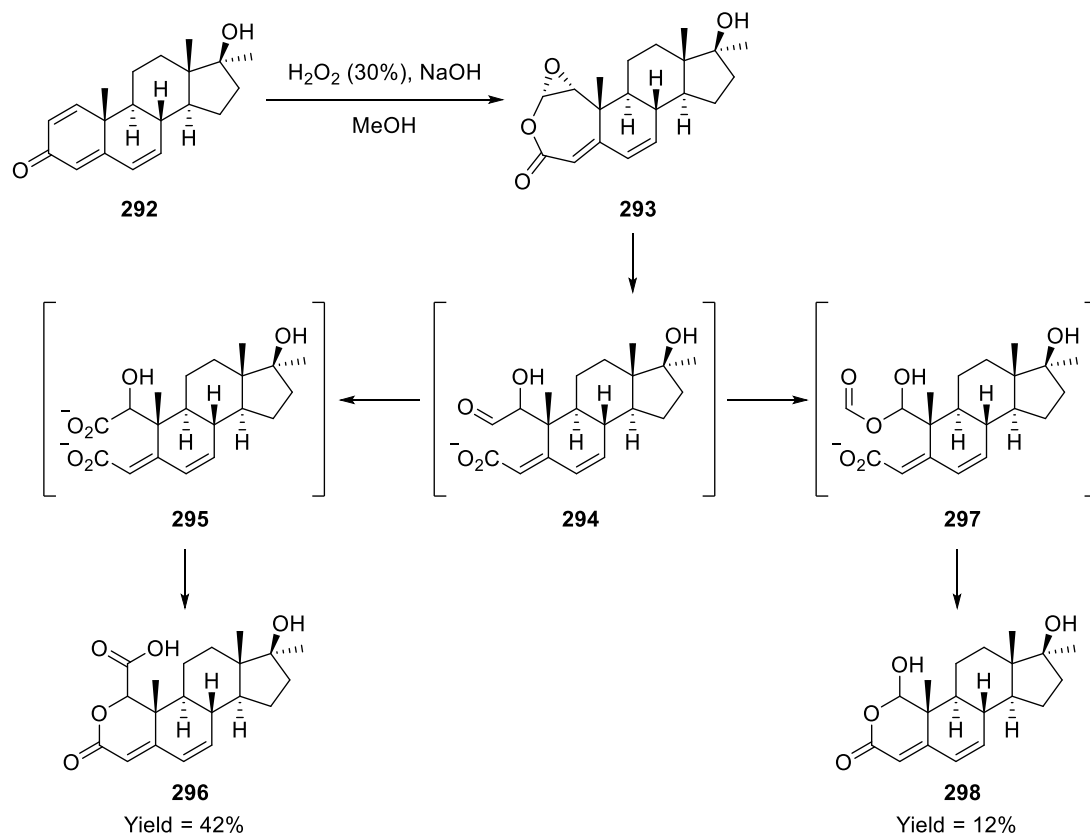
Epoxy esters are particularly amenable to rearrangement, which may be promoted by hydrolysis, as described, or alternatively may occur *via* an acid promoted intramolecular process.²⁴² In this context, investigations performed by DeBoer *et al.* revealed that the distribution of products obtained from the oxidation of $\Delta^{1(9)}$ -octalone-2 (**288**) was dependent upon the strength of the carboxylic acid by-product (Scheme 144).³⁶² Specifically, reactions performed with two equivalents of *m*CPBA provided epoxy ester **289** as the sole product, whilst oxidations with trifluoroperacetic acid resulted in a complex mixture of reaction products.³⁶² The highly acidic trifluoroacetic acid by-product was found to promote the rearrangement of epoxy lactone **289** to aldehyde lactone **290**.³⁶² Interestingly, the authors reported that aldehyde lactone **290** could then participate in a further Baeyer-Villiger oxidation to afford formate species **291**, with 66% selectivity achieved using three equivalents of trifluoroperacetic acid (TFPAA).³⁶² Therefore, as well as competing epoxidation reactions, the peracid oxidant can also promote other undesired oxidations, such as further Baeyer-Villiger oxidations.²⁴²



Scheme 144. Potential rearrangement of epoxy esters and subsequent oxidation.³⁶²

Aldehydes are particularly susceptible to oxidation either to the formate ester, as illustrated in the previous example, or to the corresponding carboxylic acid.²⁴² Secondary oxidations of this kind were reported by Kocór *et al.* to account for the formation of acid species **296** and hydroxy-lactone **298** from the treatment of steroidal ketone **292** with basic hydrogen peroxide solution (Scheme

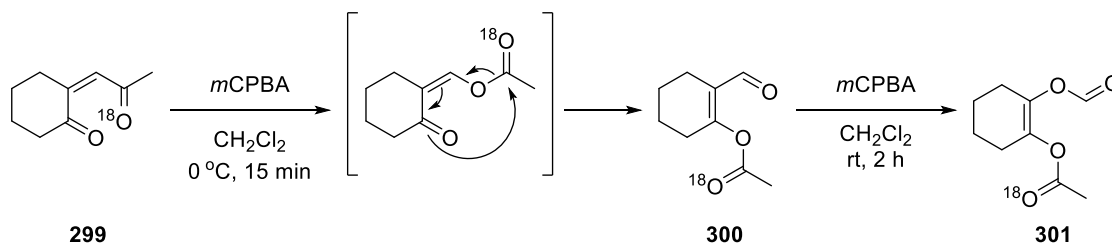
145)^{242,363} The authors proposed that *in situ* generated epoxy lactone **293** could undergo ring opening and subsequent tautomerisation to afford intermediate **294**.^{242,363} This aldehyde intermediate (**294**) may subsequently undergo a further Baeyer-Villiger oxidation to generate either acid intermediate **295** or formate ester species **297**, depending on which substituent migrates.^{242,363} Ring closure of acid intermediate **295** gives the corresponding acid substituted lactone **296**, whilst formate elimination *via* hydrolysis of **297** and successive ring closure provides the hydroxyl substituted lactone **298**.^{242,363}



Scheme 145. Formation and subsequent oxidation of aldehyde **294**.^{242,363}

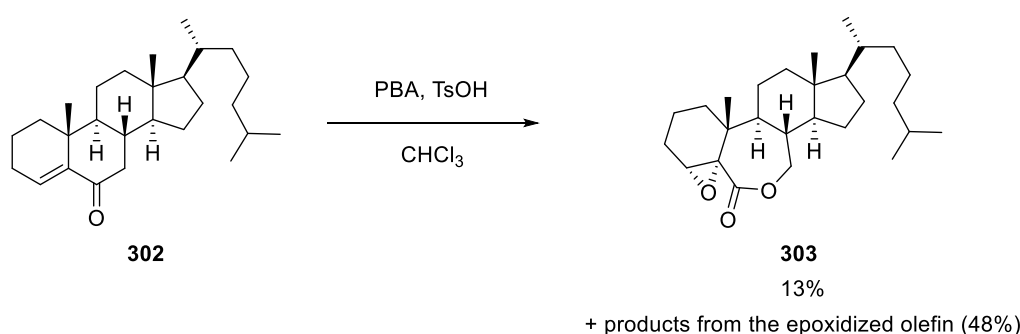
Similarly, a mechanism involving consecutive Baeyer-Villiger oxidation, rearrangement and further Baeyer-Villiger oxidation has been proposed by Jennings and Gingerich for the high yielding synthesis of formate **301** from enedione **299** by treatment with *m*CPBA (Scheme 146).^{242,364} Such a sequence of transformations accounts for the position of the ^{18}O label and acyl transfer of the nature suggested for the second step has previously been documented.³⁶⁴ Baeyer-Villiger oxidation of aldehyde **300** to generate formate **301** was again reported to be particularly facile.³⁶⁴ This example further highlights the difficulty of terminating the reaction after the initial Baeyer-Villiger oxidation and preventing subsequent undesired transformations, which result in degradation of the desired vinyl ester.²⁴² Whilst chemoselective Baeyer-Villiger

oxidations have been reported, undesired oxidation of other existing carbonyl moieties present within the starting material or intermediates can be problematic.²⁴²



Scheme 146. Consecutive Baeyer-Villiger oxidation, rearrangement and further Baeyer-Villiger oxidation of **299**.³⁶⁴

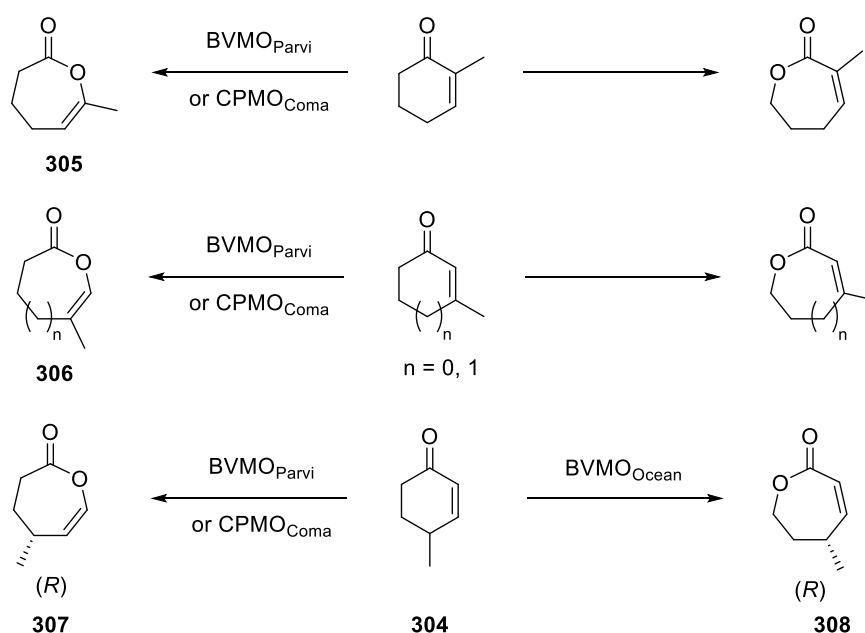
A further limitation inherent to the Baeyer-Villiger oxidation is the potential for the alternative, undesired regioisomeric ester to be formed, with the ratio of regioisomers governed by the relative migratory aptitudes and reaction conditions.²⁴² This is exemplified in the perbenzoic acid (PBA) oxidation of fused cycloalkenone **302** performed by Ahmad and Siddiqi, for which **303** was formed as the sole Baeyer-Villiger oxidation product from preferential migration of the methylene group (Scheme 147).^{242,365} However, this represents an exception rather than the rule for the relative migratory aptitude observed within the peracid oxidations of cycloalkanones, as vinyl migration is typically favoured for this substrate class.²⁴² Interestingly, selective migration of the vinyl group has also been reported for the related Criegee-type rearrangement of secondary allylic hydroperoxides to enol ethers.^{242,366} Due to the limited success expanding the Baeyer-Villiger methodology to α,β -unsaturated ketones, few successful examples exist and competition experiments have not been performed.²⁴² Thus, the exact position of a vinyl group within the migratory aptitude scale has not yet been established.²⁴²



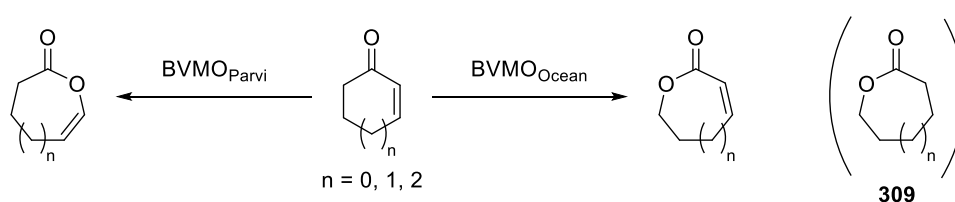
Scheme 147. Preferential methylene group migration in the perbenzoic acid oxidation of **302**.^{242,365}

With few exceptions, Baeyer-Villiger monooxygenases are ineffective at catalysing the oxidation of α,β -unsaturated ketones.³⁶⁷ The most promising biocatalysts published to date are BVMO_{Parvi}, BVMO_{Ocean} and CPMO_{Coma}, which were reported by Alphand and co-workers for the oxidation of methyl substituted cycloalkenones (Scheme 148).^{367,368} In this instance, the regioselectivity was dependent upon the enzyme used, with BVMO_{Parvi} and CPMO_{Coma} forming enol-lactones **305-307**

and BVMO_{Ocean} affording conjugated ene-lactone **308**.³⁶⁷ Enol lactones **305** and **306** were generated in good to excellent yields using BVMO_{Parvi} or CPMO_{Coma}, as determined by GC analysis (70-85%).³⁶⁷ More significantly, enantioselective oxidation of **304** with BVMO_{Parvi} or CPMO_{Coma} generated **307** in poor yield (15% and 30% respectively) but high enantioselectivity (93% *ee* and 68% *ee* respectively), with the (*R*) enantiomer being oxidised preferentially.³⁶⁷ Although BVMO_{Ocean} provided the opposite regioisomer **308**, the same enantiopreference (*R*) was reported (35% yield, 88% *ee*).³⁶⁷ Whilst competing epoxidation was not observed, unsubstituted cycloalkenones suffered from the formation of saturated lactone by-products of the form **309** (Scheme 149).³⁶⁷

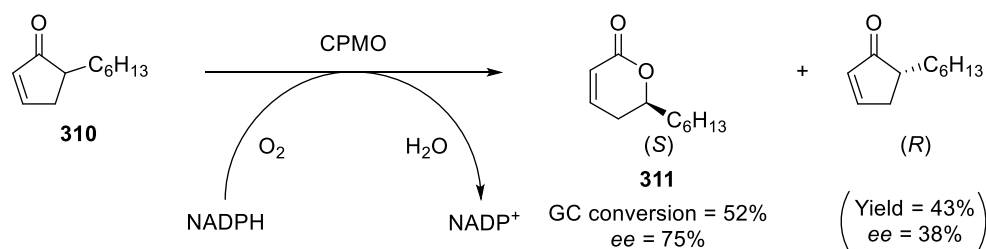


Scheme 148. Biocatalytic Baeyer-Villiger oxidation of methyl substituted cycloalkenones.³⁶⁷



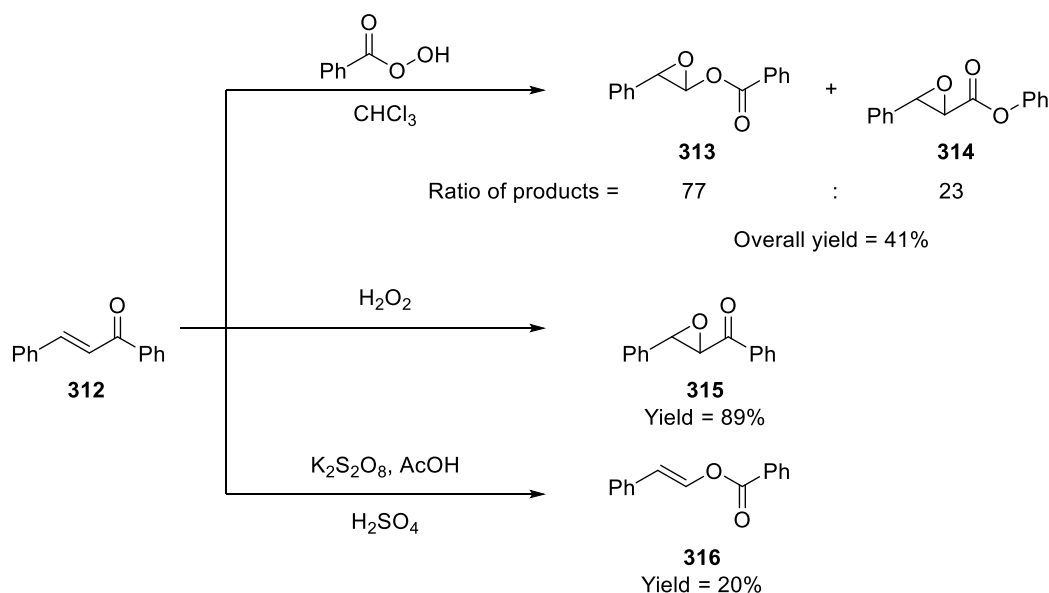
Scheme 149. Formation of undesired saturated lactone by-products.³⁶⁷

Interestingly, Willetts *et al.* previously found that CPMO catalysed the oxidation of 5-hexyl-2-cyclopenten-1-one (**310**) with the opposite regioselectivity; generating conjugated ene-lactone **311** in 52% conversion by GC and 75% *ee* (Scheme 150).³⁶⁸ In general, the use of enzymes is currently restricted to a select few cycloalkenones often with specific substitution patterns.^{367,368}



Scheme 150. CPMO catalysed oxidation of 5-hexyl-2-cyclopenten-1-one (**310**).³⁶⁸

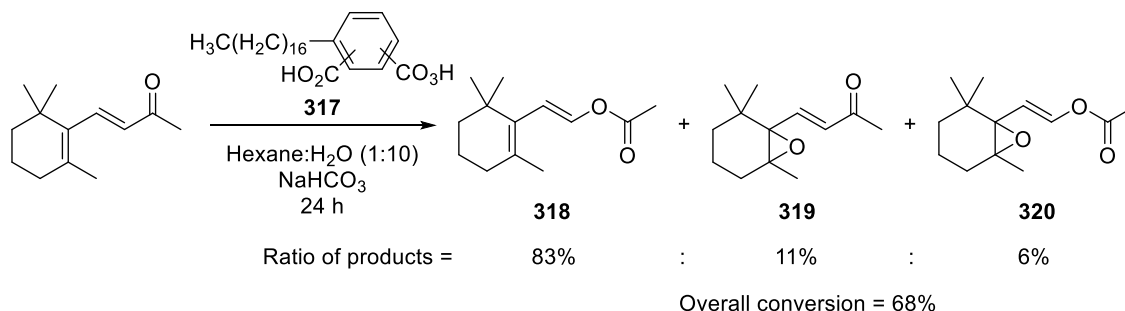
It has been determined that the distribution of oxidation products between epoxy ketone, epoxy ester and desired vinyl ester is dependent upon i) the identity and quantity of the oxidant employed, ii) the acidity of the reaction medium and iii) the identity of the substrate.^{242,350,353,362} The efforts of several groups have been focussed on trying to improve the selectivity of the oxidation for the vinyl ester species. For instance, Yokoyama and Nohara reported that the perbenzoic acid promoted oxidation of chalcone **312** results in a mixture of regioisomeric epoxy ester species **313** and **314**, whilst epoxy ketone **315** was obtained by Weitz and Scheffer in 89% yield using hydrogen peroxide as the oxidant (Scheme 151).^{242,369-371} Subsequently, Dhar *et al.* developed the peroxydisulfate based system, which achieves some selectivity for the Baeyer-Villiger oxidation product **316**, albeit in low isolated yield (Scheme 151).^{242,369,370} This method was applied to a handful of chalcone derivatives with similar success (3 examples, 19-37% yield).³⁶⁹



Scheme 151. Effect of the oxidant on the distribution of products generated from the oxidation of **312**.^{242,369-371}

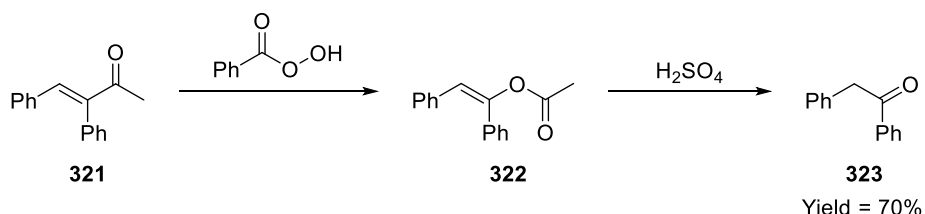
Fujise and co-workers similarly determined that substitution of peroxy acids, such as perbenzoic acid and *m*CPBA, for the surfactant based oxidising agent 3-heptadecyl-monoperphthalic acid **317**, allowed for **318** to be formed with relatively high selectivity (Scheme 152).³⁷² Crucially,

epoxidation of the endocyclic olefin was found to be minimised.^{242,372,373} As a reference, 54% conversion exclusively to epoxyketone **319** was observed using *m*CPBA in the presence of sodium dodesylsulfate,³⁷² whilst Isoe *et al.* reported exclusive formation of epoxy ester **320** with two equivalents of perbenzoic acid.³⁷³



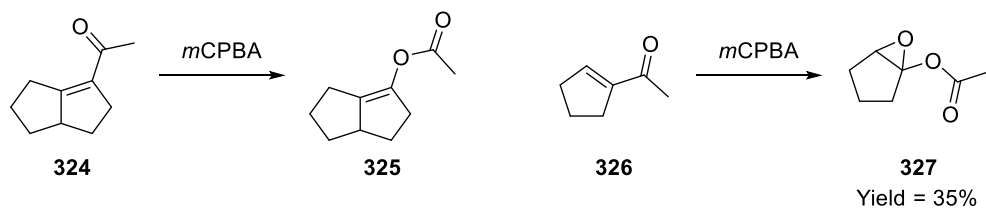
Scheme 152. Improved selectivity for the Baeyer-Villiger product **318**.^{242,372}

Nevertheless, organic peracids have been successfully applied within the Baeyer-Villiger oxidation of α,β -unsaturated ketones to afford the corresponding vinyl esters in relatively high selectivity. An example of this was reported by Yokoyama and Nohara, which specifically entailed the perbenzoic oxidation of ketone **321** (Scheme 153).³⁷⁰ Vinyl ester **322** was formed in high yield (70%) from competitive migration of the vinyl group, as can be inferred from the isolated mass of the hydrolysed species **323**.³⁷⁰ Conversely, the oxidation of chalcone resulted in a mixture of benzoic acid and phenol upon hydrolysis; corresponding to both phenyl and vinyl migration.³⁷⁰ The observed migratory aptitudes were consistent with those previously reported by Böesecken and co-workers.^{370,374,375}



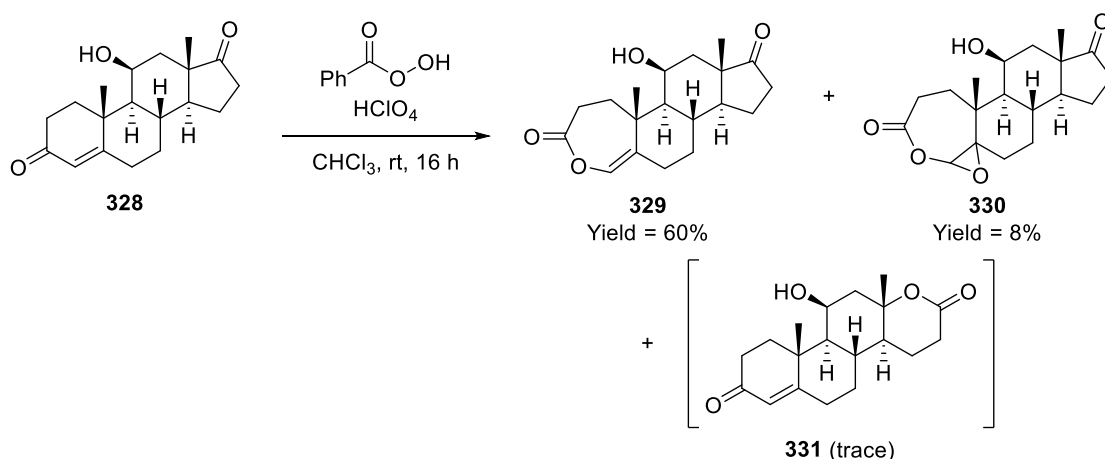
Scheme 153. Preferential vinyl group migration in the perbenzoic acid oxidation of **321**.³⁷⁰

In addition to acyclic conjugated ketones, application of the Baeyer-Villiger oxidation to fused-ring and mono-cyclic systems involving both endo- and exocyclic double bonds has also been met with some success.²⁴² For instance, fused ring system **324** was reportedly oxidised to the corresponding enol acetate **325** using *m*CPBA, whilst the oxidation of cyclopentenyl ketone **326** surprisingly gave exclusively the epoxyacetate **327** in 35% yield using the same oxidant (Scheme 154).^{242,359,376}



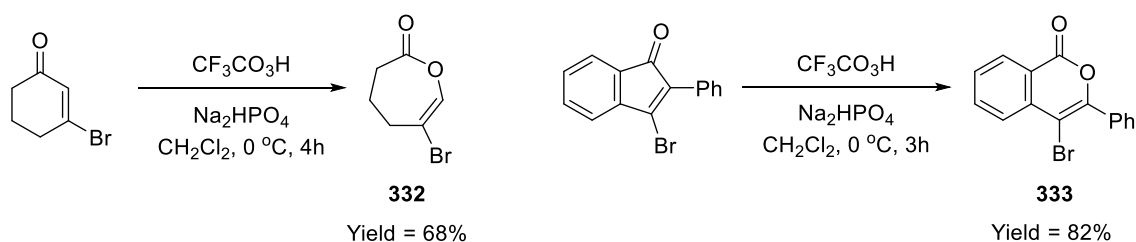
Scheme 154. *m*CPBA mediated oxidations to form esters **325** and **327**.^{359,376}

Caspi and co-workers have demonstrated that chemoselective oxidation of a conjugated, unsaturated ketone in the presence of a saturated ketone is possible.^{242,377} Specifically, unsaturated lactone **329** was afforded in moderate yield (60%) from the oxidation of androst-4-en-3,17-dione **328** using perbenzoic acid in the presence of perchloric acid, with only small quantities of the corresponding epoxylactone **330** isolated (Scheme 155).^{242,377} Interestingly, the alternative lactone product **331**, resulting from oxidation at the C17 carbonyl, was believed to be formed in only trace quantities.^{242,377} As highlighted by this example, for such cyclic enones migration of the vinyl group typically occurs in preference to oxygen insertion adjacent to the methylene carbon of the ring.²⁴²



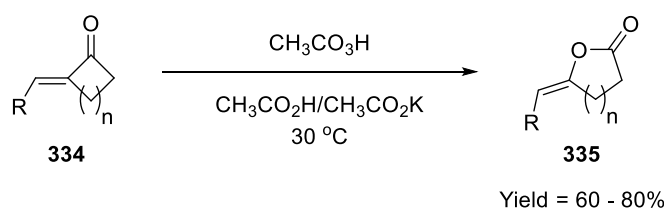
Scheme 155. Selective Baeyer-Villiger oxidation of α,β -unsaturated ketone **328** using perbenzoic acid.^{242,377}

Halo enol lactones, such as **332** and **333**, can also be prepared by the Baeyer-Villiger oxidation of β -halo cycloenones using trifluoroperacetic acid, which similarly relies on the greater migratory aptitude of the vinyl group relative to the primary alkyl group (Scheme 156).^{242,378} Surprisingly, this phenomenon was unaffected by the electron withdrawing nature of the halide substituent, which may be anticipated to reduce the ability of the vinyl group to stabilise the forming positive charge.^{242,378} This methodology allows for the desired halo enol lactones to be generated in high yields without any competing epoxidation, which the authors have attributed to the highly acidic reaction conditions, although it is curious to note that a buffer is employed.^{242,378}



Scheme 156. Baeyer-Villiger oxidation of β -halo cycloenones using trifluoroacetic acid.^{242,378}

Often, the oxidation conditions published have only been explored for one specific compound, which may be a key intermediate in a multi-step synthetic route.³⁷⁹ However, Walton explored the generality of the peracetic acid oxidation for a series of exocyclic enones of general structure **334**, with high to excellent yields achieved (60-80%) (Scheme 157).^{242,350} Within these reactions it was found that tuning the acidity of the medium was crucial for achieving superior yields.³⁵⁰ Interestingly, oxidations performed in acetic acid saturated with potassium acetate, which represented the least acidic media tested, gave the best selectivity and yield of the desired enol lactone **335**.³⁵⁰ This methodology was subsequently applied by Silverstein *et al.* for the synthesis of keto acids and keto esters.³⁸⁰



Scheme 157. Baeyer-Villiger oxidation of exocyclic enones using peroxyacetic acid.^{242,350}

Isolated reports therefore exist within the literature of the Baeyer-Villiger oxidation being applied to α,β -unsaturated ketones, typically with preferential migration of the vinyl group observed.²⁴² Although high yields and chemoselectivity can be achieved in some instances, the methodologies developed are typically substrate specific and may suffer from competing epoxidation reactions in addition to other side reactions.²⁴² It has been determined that the distribution of products obtained is dependent upon the oxidant, substrate and acidity of the media employed.^{242,350}

2.2 Project Aims

Despite the advances made towards a successful protocol for the selective Baeyer-Villiger oxidation of α,β -unsaturated ketones, the current methods often lack substrate generality and in many cases still suffer from low yields and complex mixtures of reaction products.²⁴² Therefore, it was proposed that by identifying a catalytic system that could selectively promote the desired nucleophilic transformation, the aforementioned problems could be overcome and vinyl ester synthesis improved. Specifically, we were interested in the ability of organocatalysts to promote this transformation, due to their advantageous properties, such as low toxicity, ease of handling and being inexpensive, as well as their importance within the field of green chemistry.^{381,382}

Baeyer-Villiger oxidations performed with peracids in non-polar solvents proceed *via* a concerted, non-ionic mechanism.^{230,280,291,321,326,327} As proton transfer occurs during heavy atom reorganisation in both the addition and migration transition states (Figure 24),^{230,232,280,281,326} it can be inferred that proton transfer occurs during the rate-determining step. Therefore, there is the potential to catalyse the Baeyer-Villiger oxidation by facilitating the proton transfer events, which accounts for the catalysis observed in the presence of adventitious carboxylic acid.^{294,295,297,323-325} The carboxylic acid essentially functions as a proton shuttle; accepting a proton onto the carbonyl functionality, whilst simultaneously donating its acidic proton.^{230,233,280,281,292,296} Precedent therefore exists for simultaneous general acid-general base catalysis within the Baeyer-Villiger oxidation.

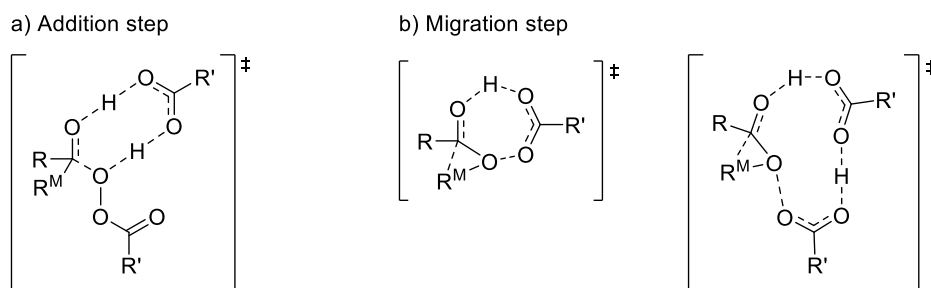
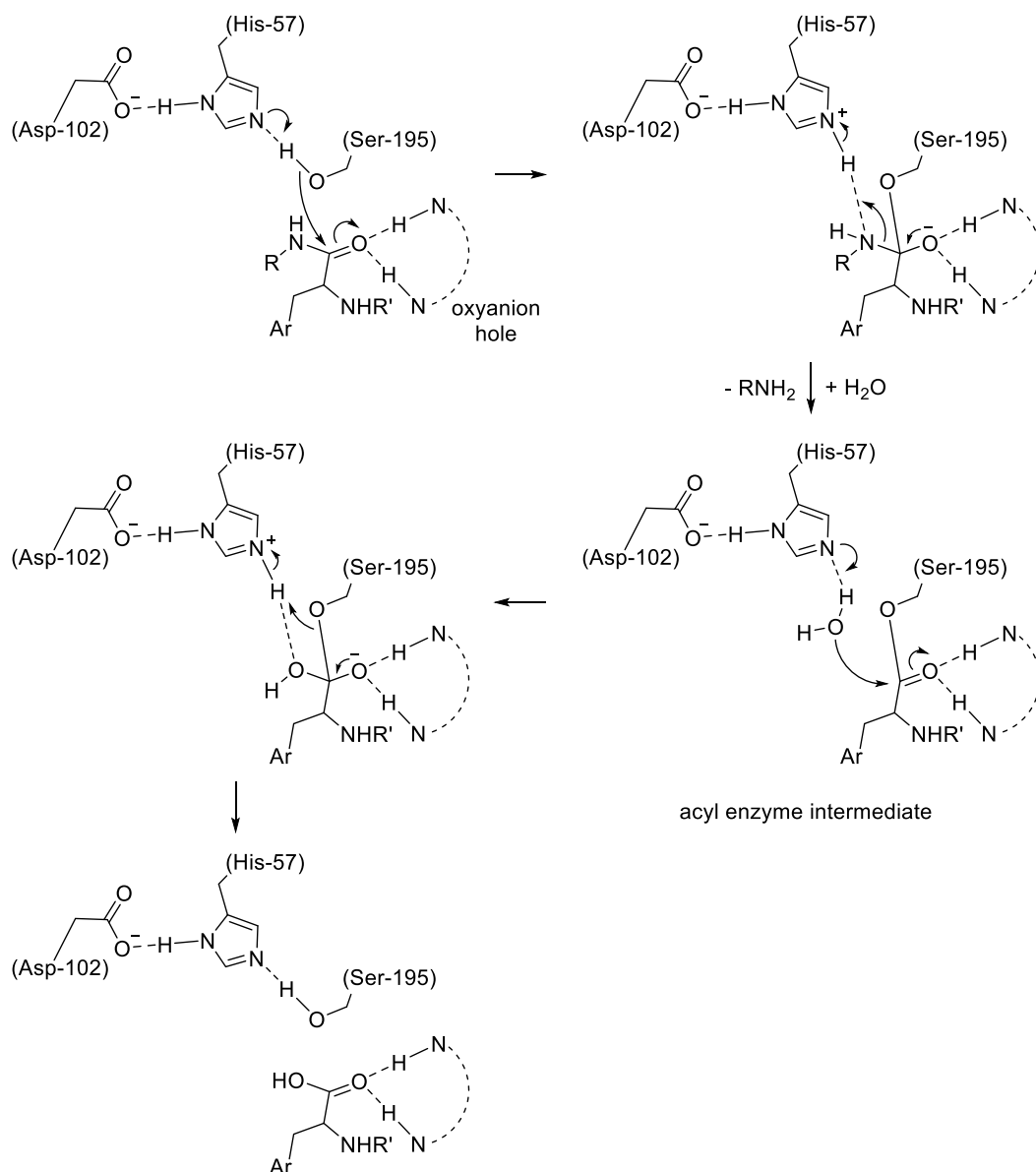


Figure 24. Concerted proton transfer pathways reported for Baeyer-Villiger oxidations performed in non-polar solvents in the presence of carboxylic acids.^{280,327}

General acid-base catalysis is a strategy commonly utilised by enzymes.^{383,384} Within the enzyme's active site, a series of highly conserved amino acid residues act to stabilise the transition state *via* hydrogen bonding interactions, which can act as facile proton transfer pathways (Scheme 158).³⁸³⁻³⁸⁵ Enzymes exhibit particularly high catalytic activity due to the cooperative interactions of both acidic and basic moieties within these residues, which maximises stabilisation; permissible due to the relative positioning of these otherwise incompatible functionalities.^{386,387} This is of particular relevance for hydrolase enzymes, such as serine protease, in which basic,

acidic and nucleophilic amino acid residues (known as a catalytic triad) function synergistically to catalyse hydrolysis reactions *via* the formation of an acyl-enzyme intermediate.^{383,384,386} Specifically, proton transfer is facilitated between the three residues, which activates the nucleophilic residue, whilst the tetrahedral intermediate is stabilised by hydrogen bonding interactions within the oxyanion hole.^{383,384,386,387}



Scheme 158. Mechanism of hydrolysis by serine protease.³⁸⁷

Similar to protein enzymes, nucleobases in the hairpin ribozyme function as general acid-base catalysts to promote the cleavage of the RNA phosphodiester backbone (Figure 25).³⁸⁸ Guanine functions as a general base to enhance the nucleophilicity of the hydroxyl nucleophile *via* deprotonation, whilst adenine simultaneously acts as a general acid by protonating and stabilising the leaving group.³⁸⁸

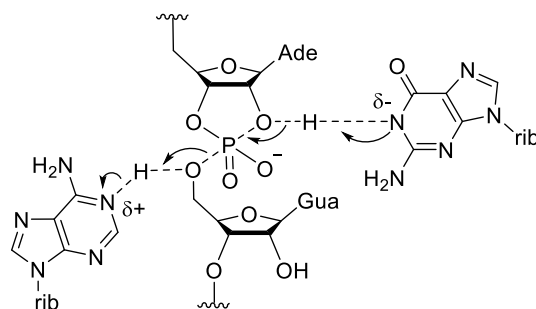


Figure 25. Nucleobases in the hairpin ribozyme functioning as general acid-base catalysts for the cleavage of RNA.³⁸⁸

However, achieving these types of catalytic proton transfer events in solution outside of the enzyme's active site can be problematic, as it is difficult to devise conditions that enables a Brønsted base to function in the presence of a Brønsted acid, without neutralisation and salt formation occurring. Due to the unavoidable presence of carboxylic acid within the reaction system, the Baeyer-Villiger oxidation precludes the use of a strong Brønsted base for facilitating proton transfer. Therefore, it was considered that a hydrogen bond acceptor may catalyse the Baeyer-Villiger oxidation by promoting the kinetically significant proton transfer event *via* the formation of hydrogen bonds; reminiscent of the stabilising interactions operating within enzymes.^{221,389,390} A weak Brønsted base that is a good hydrogen bond acceptor capable of forming short, strong hydrogen bonds were identified as prerequisites for a suitable catalyst. The energy barrier to proton transfer along such hydrogen bonds should theoretically be reduced.^{221,390,391}

One class of compound that fulfil these criteria are *N*-oxides. *N*-Oxides are weakly basic and it is therefore anticipated that they will exist primarily in their unprotonated form under the acidic reaction conditions. As a reference, the pK_a of the conjugate acid of pyridine *N*-oxide is 0.79 in water, whilst the conjugate acid of the parent amine has a pK_a of 5.23 (Figure 26).³⁹² Additionally, from the hydrogen bond basicity scale (pK_{BHX}) developed by Laurence and co-workers, which is a measure of a species ability to act as a hydrogen bond acceptor, *N*-oxides have been classified as strong or very strong hydrogen bond acceptors depending on their exact nature (strong: $1.8 < pK_{BHX} < 3$, very strong: $pK_{BHX} > 3$).^{221,393,394} For instance, pyridine *N*-oxide has a pK_{BHX} of 2.72 (*cf.* pyridine $pK_{BHX} = 1.86$) and the pK_{BHX} of trimethylamine *N*-oxide is 5.46 (*cf.* trimethylamine $pK_{BHX} = 2.13$).^{393,394} It should be noted that hydrogen bond basicity does not parallel Brønsted basicity.^{393,394} Literature precedent also exists for hydrogen bonding interactions and the formation of hydrogen bonded complexes between *N*-oxides and various hydrogen bond donors, such as carboxylic acids and alcohols.³⁹⁵⁻³⁹⁹ Thus, *N*-oxides are capable of forming short, strong hydrogen bonds, which would be expected to lower the barrier to proton transfer.^{391,399,400} Despite

their advantageous physical properties, *N*-oxides are largely unrepresented within the arena of hydrogen bond catalysis.²¹⁸⁻²²²

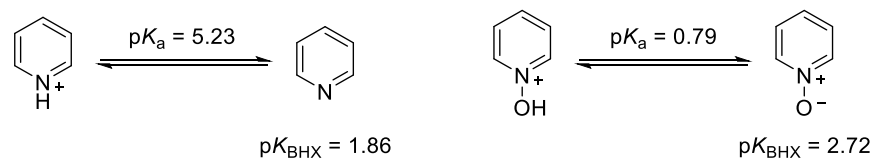
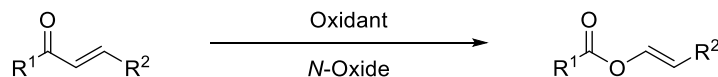


Figure 26. Relative pK_a and pK_{BHX} values of pyridine and pyridine *N*-oxide.³⁹²⁻³⁹⁴

Therefore, the aim of this work is to investigate the potential of *N*-oxides to function as hydrogen bond catalysts within the Baeyer-Villiger oxidation of α,β -unsaturated ketones (Scheme 159); imitating the proton transfer processes that occur in nature. This study holds two-fold significance, as it is hoped that: 1) the small portfolio of reactions employing *N*-oxides as novel hydrogen bond catalysts can be extended and 2) a methodology can be developed that improves the efficiency and selectivity of the Baeyer-Villiger oxidation for the synthesis of vinyl esters, with a broader substrate generality. Additionally, this study will enable us to extract further information on the mechanism of the Baeyer-Villiger oxidation, which has not yet been fully elucidated. This is particularly true with regards to which step is rate determining and what influences this as well as the relative migratory aptitude of a vinyl group.



Scheme 159. Proposed strategy for promoting the Baeyer-Villiger oxidation of α,β -unsaturated ketones.

2.3 Results and Discussion

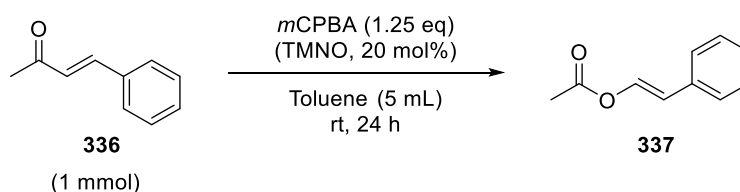
2.3.1 Proof of principle

Initial studies were focussed on determining whether *N*-oxides exhibit any catalytic activity within the Baeyer-Villiger oxidation of (*E*)-4-phenyl-3-buten-2-one (**336**) to (*E*)-2-phenylethenyl acetate (**337**), for which competitive migration should be prevented due to the poor migratory aptitude of the methyl group (Table 4).^{228,242,275} In order to implement this strategy, suitable reaction conditions needed to be devised to promote the desired hydrogen bonding interactions and facilitate proton transfer. From the hydrogen bond basicity scale developed by Laurence and co-workers, trimethylamine *N*-oxide was identified as an extremely good hydrogen bond acceptor ($pK_{\text{BHX}} = 5.46$) and consequently its ability to act as a catalyst was explored.^{393,394} This approach precludes the use of strong acids, which can additionally promote undesired side reactions and product degradation, but requires a relatively reactive peracid:acid combination.²⁴² Therefore, based on its oxidising ability and relative acidity of the corresponding acid, *m*CPBA was selected as the oxidant (relative oxidising ability: trifluoroperacetic acid > monopermaleic acid > mono-*o*-perphthalic acid > 3,5-dinitroperbenzoic acid > *para*-nitroperbenzoic acid > *meta*-chloroperbenzoic acid (*m*CPBA) \approx performic acid > perbenzoic acid > peracetic acid >> hydrogen peroxide > *tert*-butylhydrogen peroxide).²³⁸ It was anticipated that the use of this peracid may also limit any competing epoxidation reactions.²⁴² Furthermore, unlike the majority of other organic peracids, *m*CPBA benefits from being commercially available in particularly high purity ($\leq 77\%$), is easy to handle and relatively inexpensive.^{272,401} It is these properties that make *m*CPBA a popular choice of oxidant for the Baeyer-Villiger oxidation.^{272,401} It has been reported that proton transfer occurs in concert with heavy atom reorganisation for both steps of the Baeyer-Villiger oxidation in non-polar, aprotic organic solvents, which resembles the conditions found within the hydrophobic pocket of an enzyme's active site.^{230,232,280,281,326,390} Such conditions may promote the formation of short, strong hydrogen bonds along which facile proton transfer may occur.^{389-391,399} Toluene was therefore considered a suitable solvent, as it fulfils this criteria and is also relatively effective at solubilising *m*CPBA. Specifically, the reactions were performed at room temperature without air exclusion for 24 hours.

Pleasingly, trimethylamine *N*-oxide was found to greatly improve the efficiency and chemoselectivity of the oxidation for the formation of the desired vinyl ester **337** relative to the uncatalysed system, with 77% selectivity achieved in the presence of the catalyst relative to only 30% without (Table 4, entries 1 and 2). In both instances, this methodology afforded the vinyl acetate, which corresponds to preferential migration of the styryl moiety, rather than the regioisomeric methyl ester, as evidenced by the absence of a characteristic singlet at 3.81 ppm

within the ^1H NMR spectra.⁴⁰² Furthermore, the distinctive upfield doublet appearing at 6.39 ppm and the large coupling constant of 12.8 Hz observed between the vinyl protons is indicative of a *trans* configuration, in accordance with the Karplus relationship.^{328,329} Therefore, the oxidation proceeded with retention of stereochemistry, providing exclusively the *E*-stereoisomer. However, as can be seen from the results in Table 4, multiple by-products were also formed alongside vinyl ester **337**, particularly in the absence of the *N*-oxide. The presence of the catalyst therefore influences the product distribution and provides a much cleaner reaction profile, being selective for the desired oxidation (Figure 27).

Table 4. Examining the catalytic potential of TMNO within the Baeyer-Villiger oxidation of (*E*)-4-phenyl-3-buten-2-one (**336**) with *m*CPBA.



Entry	Catalyst	Ket. 336	Ester 337	Epox. 339	Ald. 341	Form. 354	Epox. 338
1	-	34	30	15	13	4	4
2	TMNO	7	77	8	6	-	2

Product ratios were determined by ^1H NMR spectroscopic analysis.

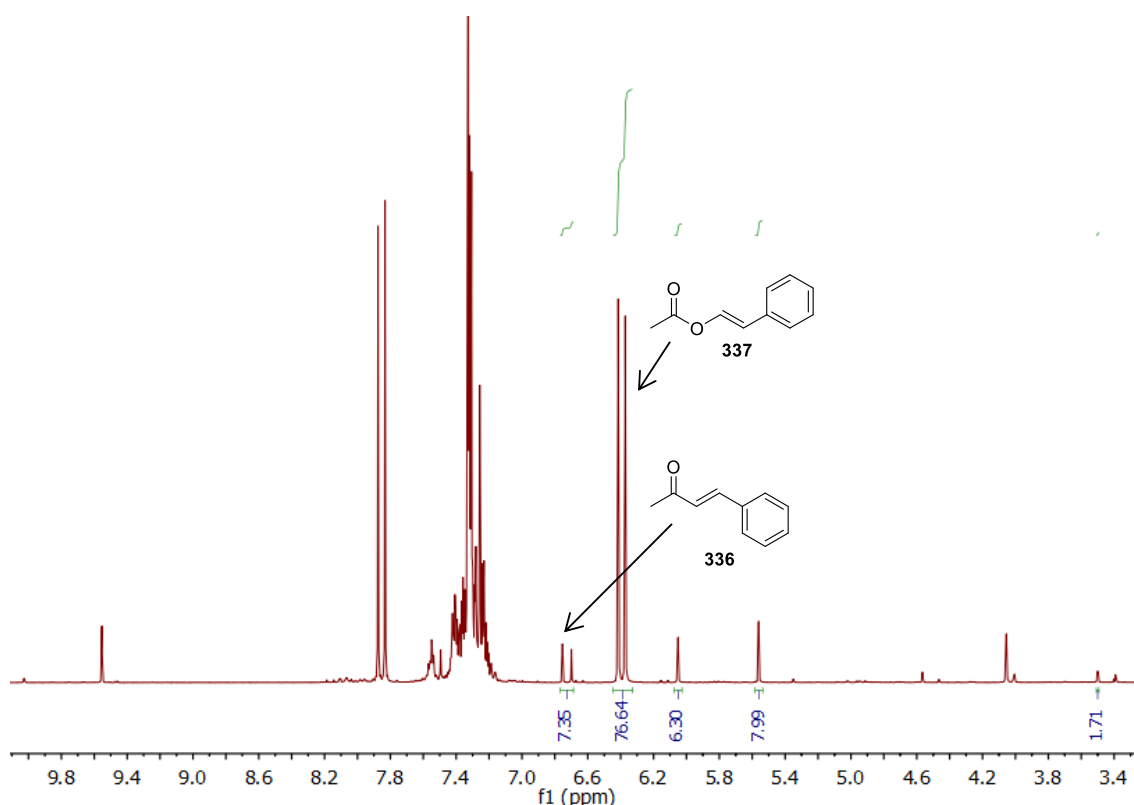


Figure 27. 300 MHz ¹H NMR spectrum obtained in CDCl₃ for the crude TMNO reaction mixture post aqueous work-up.

2.3.2 By-product isolation and characterisation

Significant peaks were observed in the ¹H NMR spectra for the crude reaction mixtures post aqueous work-up, which could not be attributed to either the starting material **336** or vinyl ester **337**, as highlighted in Figure 28 for the uncatalysed variant. The characteristic peaks ascribed to each by-product is indicated with a different colour. Epoxy ketone **338** (highlighted in purple) and epoxy ester **339** (highlighted in orange) were identified from the characteristic pairs of doublets at 4.01 and 3.50 ppm for the former and 5.56 and 4.06 ppm for the latter species, which can be assigned to the vicinal epoxide protons (Scheme 160). It was deduced that the epoxides possess *trans*-stereochemistry based on the small vicinal coupling constants of 1.8 and 0.8 Hz for the epoxy ketone and epoxy ester respectively. The identity and stereochemistry of these species was confirmed by comparison of the characteristic ¹H NMR peaks with literature data.^{403,404}

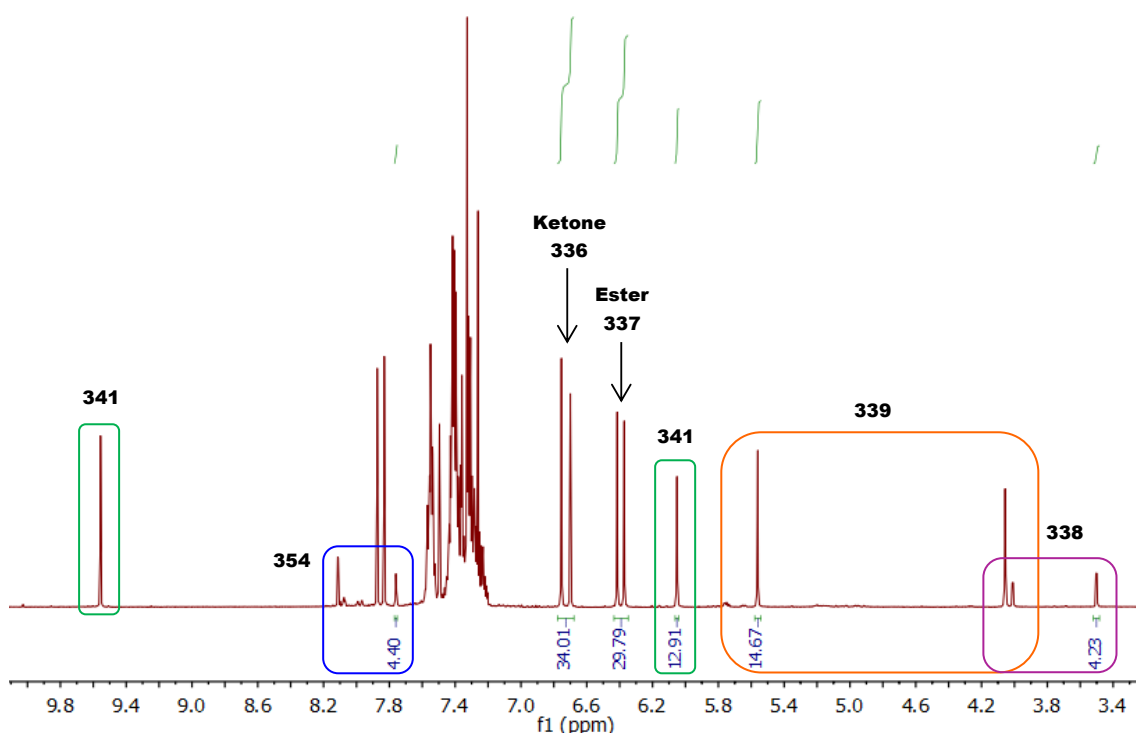
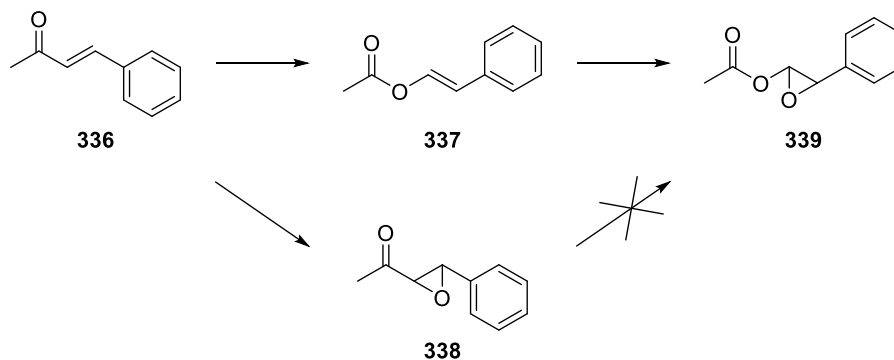


Figure 28. 300 MHz ^1H NMR spectrum obtained in CDCl_3 for the crude uncatalysed reaction mixture post aqueous work-up.

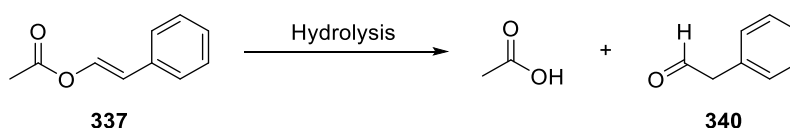


Scheme 160. Proposed pathways for the formation of epoxy ketone 338 and epoxy ester 339.

Unfortunately, these species were not successfully isolated, as they were only formed in small quantities and are inherently unstable due to their propensity to undergo ring opening reactions.^{405,406} Such epoxides are, however, commonly reported as undesired oxidation products within the Baeyer-Villiger reaction of unsaturated substrates.^{242,349} For oxidations performed with peracids, previous studies have concluded that epoxy esters are typically formed from epoxidation of the vinyl ester rather than Baeyer-Villiger oxidation of the epoxy ketone and it is thought that this can be extended to this system (Scheme 160).^{242,349} As anticipated, *m*CPBA promoted the Baeyer-Villiger oxidation of (*E*)-4-phenyl-3-buten-2-one (**336**) in preference to epoxidation of

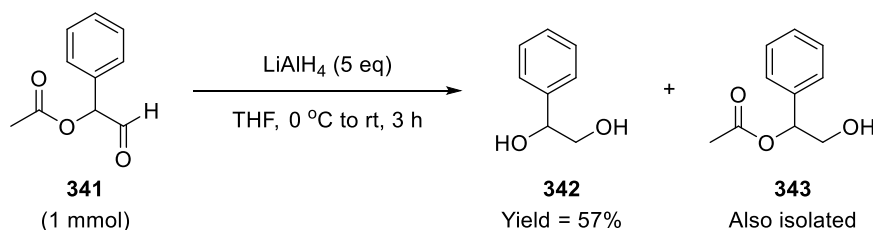
the electron poor olefin moiety, with only trace quantities of the epoxy ketone **338** observed. Additionally, the more nucleophilic, electron rich double bond of the vinyl ester appears to undergo more facile epoxidation than the olefin portion of the corresponding α,β -unsaturated ketone.

The singlet at 9.56 ppm, as highlighted in green (Figure 28), is characteristic of an aldehydic proton. It was initially considered feasible that 2-phenylacetaldehyde (**340**) may have been generated from irreversible hydrolysis of the vinyl ester during the aqueous work-up (Scheme 161), which is commonly reported for this functional group.^{242,328}



Scheme 161. Potential hydrolysis of vinyl ester 337.

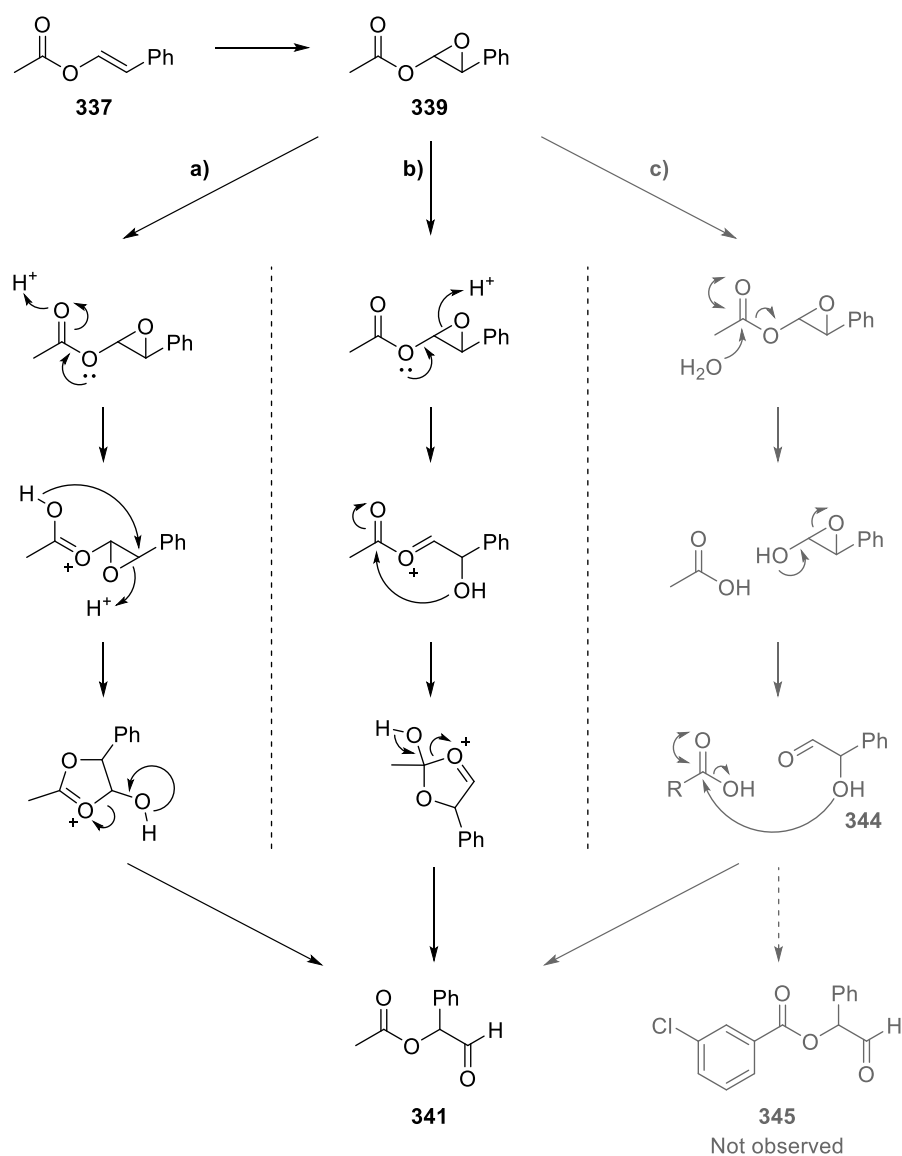
After purification by flash column chromatography and full characterisation, the spectroscopic data was found to be inconsistent with **340** and instead attributable to α -acetoxy aldehyde **341** (Scheme 162). Whilst the characterisation data was in agreement with the literature,⁴⁰⁷ to further confirm that **341** had been formed as a by-product, the isolated aldehyde impurity was reduced to the corresponding diol (Scheme 162). A tetrahydrofuran solution of the aldehyde species was slowly treated with five equivalents of lithium aluminium hydride at 0 °C and then stirred for a further three hours at room temperature.⁴⁰⁸ Upon work-up and purification by flash column chromatography the anticipated 1,2-diol **342** was isolated in 57% yield, with an analytically pure sample of the mono-reduction product **343** also obtained; thus confirming the identity of the aldehyde as **341**. Therefore, this may represent a useful method for the synthesis of novel α -acetoxy aldehydes and allow access to their corresponding 1,2-diols.



Scheme 162. Reduction of α -acetoxy aldehyde 341 with lithium aluminium hydride.⁴⁰⁸

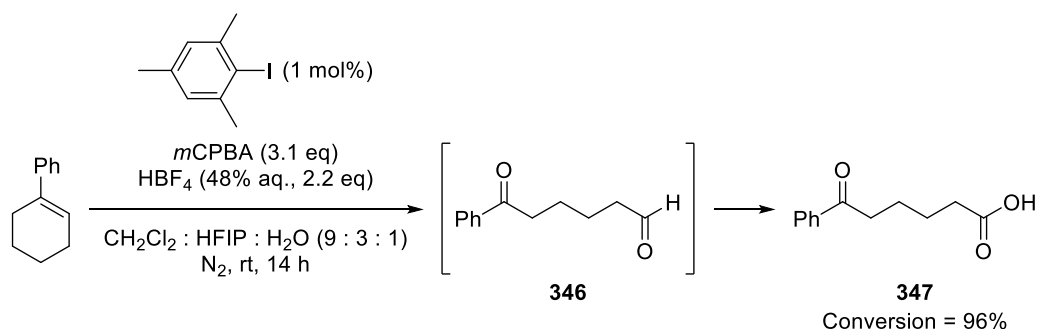
A mechanism involving initial epoxidation of vinyl ester **337** with *m*CPBA is proposed for the formation of aldehyde **341** (Scheme 163). It is postulated that under the acidic reaction conditions epoxy ester **339** may then undergo intramolecular cyclisation and rearrangement *via* either pathway a or pathway b to afford aldehyde species **341**. Hydrolysis of epoxy ester **339** followed

by acylation of the aldehyde tautomer **344** with expelled acetic acid (pathway c) was discounted on the basis that competitive acylation with *m*CBA to afford **345** wasn't observed and would be expected due to the large excess of this acidic species present. Treatment of isolated vinyl ester **337** with 1.2 equivalents of *m*CPBA for 24 hours at room temperature was found to result in the formation of epoxide **339** and aldehyde **341** among other species, which is consistent with the proposed mechanisms and also provides evidence that epoxy ester **339** is derived from the vinyl ester **337**. As highlighted previously within this chapter, such aldehyde species have been observed within peracid oxidations of α,β -unsaturated ketones, although they are often intermediates and not typically isolated.²⁴² For instance, an analogous acid catalysed rearrangement was proposed by DeBoer and co-workers to account for the observed aldehyde species formed from the trifluoroperacetic acid oxidation of $\Delta^{1(9)}$ -octalone-2.³⁶² This precedent along with the experimental findings indicate that the *N*-oxide is not required to promote this undesired transformation.



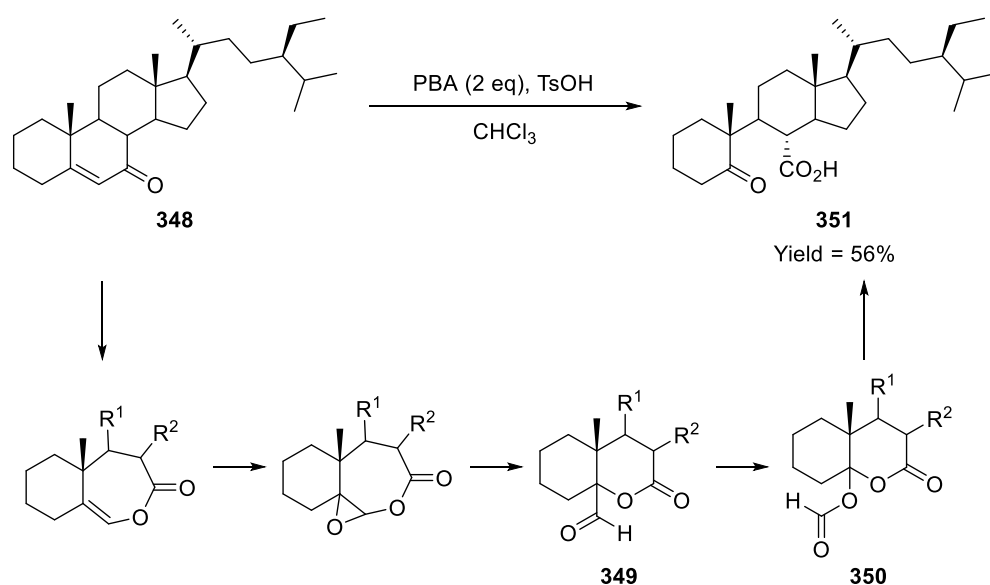
Scheme 163. Potential mechanistic pathways for the formation of α -acetoxy aldehyde **341**.

Aldehydes are readily oxidised to carboxylic acids and formate esters by *m*CPBA and other oxidants, with the exact ratio dependent upon the solvent and oxidant used.^{242,409} These high oxidation state species are commonly reported as by-products in peracid oxidations where an aldehyde is generated *in situ*.²⁴² For instance, in 2009 Ochiai *et al.* reported a novel organocatalysed oxidative cleavage of carbon-carbon multiple bonds using iodomesitylene, which employed *m*CPBA as the oxidant (Scheme 164).⁴¹⁰ Under the acidic reaction conditions and at low catalyst loadings, the resultant keto aldehyde **346** was oxidised entirely to the corresponding keto acid **347** by excess peracid reagent.⁴¹⁰



Scheme 164. *In situ* oxidation of aldehyde **346** to the corresponding carboxylic acid **347** with *m*CPBA.⁴¹⁰

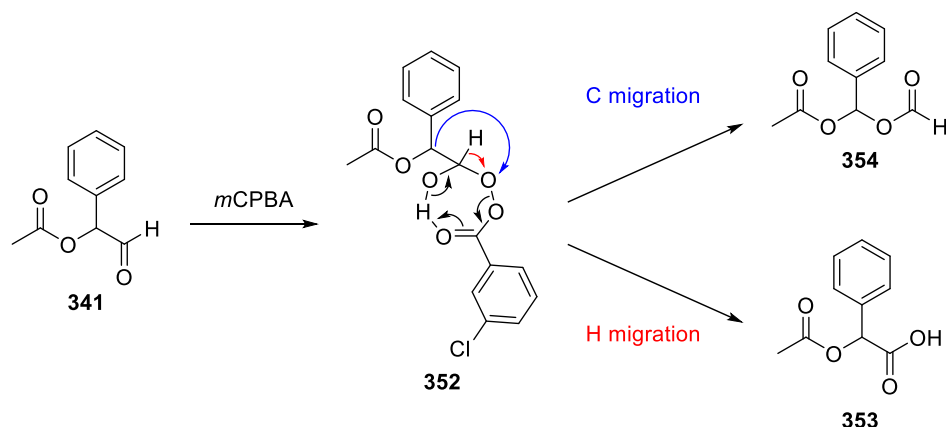
Conversely, formate ester **350** was formed as an intermediate in the oxidation of stigmasterone (**348**) to keto acid **351** from the perbenzoic acid oxidation of formyl lactone intermediate **349** (Scheme 165).^{242,411} Subsequent hydrolysis and ring opening of the formate ester then affords keto acid **351** in 56% yield.^{242,411}



Scheme 165. Oxidation of aldehyde **349** into formate ester **350**, as a key step in the synthesis of **351**.^{242,411}

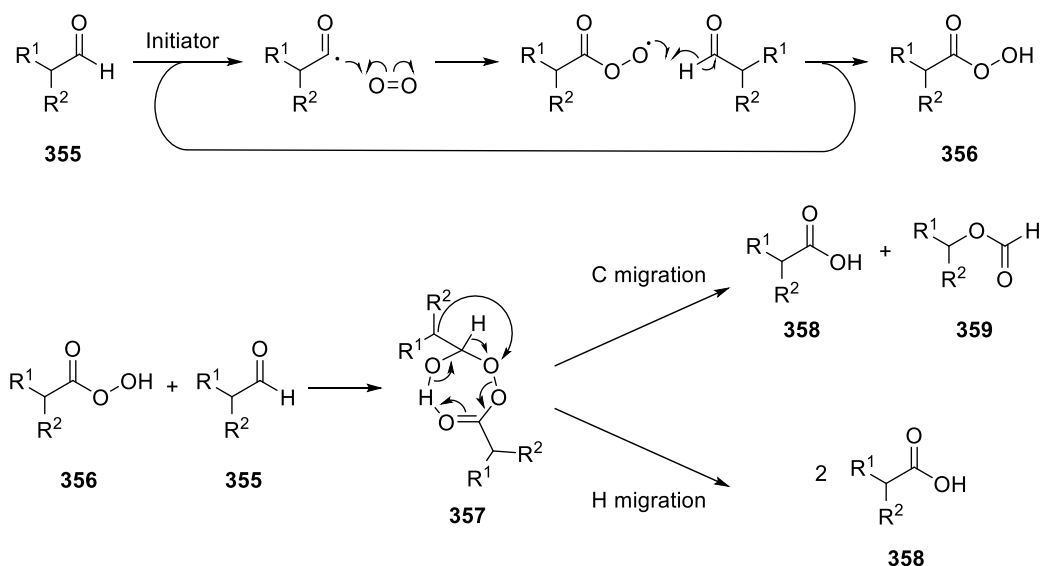
Therefore, it was unsurprising to find that both carboxylic acid **353** and formate ester **354** were often formed under the reaction conditions (Scheme 166), although in this particular instance the carboxylic acid was not observed. From Figure 28, the singlet at 7.76 ppm is attributable to formate ester **354** (highlighted in blue), whilst the carboxylic acid **353** was identified when present from a singlet appearing at 5.98 ppm within the ¹H NMR spectra. These species were again successfully isolated by flash column chromatography and fully characterised, with all data in agreement with that reported within the literature.^{412,413} Both oxidation processes proceed *via* adduct **352**, with hydrogen migration affording carboxylic acid **353** and migration of the carbon

atom giving formate ester **354**.⁴⁰⁹ In all instances, the formate ester was observed in significantly higher concentration than the carboxylic acid.



Scheme 166. Mechanism for the oxidation of aldehyde **341** to afford either acid **353** or formate ester **354**.⁴⁰⁹

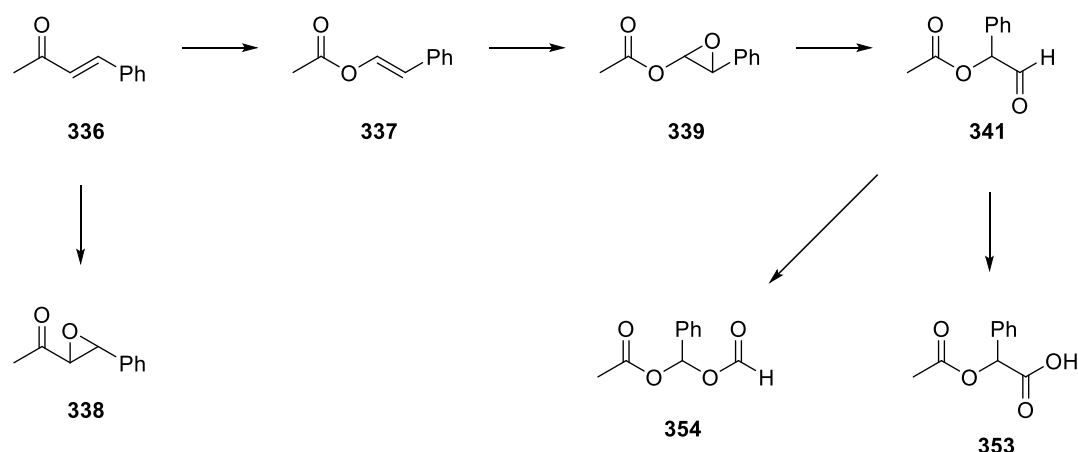
This result is in accordance with the findings of Lehtinen and co-workers, who reported that the oxidation of 2-phenylpropionaldehyde with *m*CPBA in toluene favoured the formation of the formate ester, with a product ratio of 19:1 (formate ester : carboxylic acid) observed.⁴⁰⁹ Interestingly, molecular oxygen can also promote the oxidations outlined in a similar manner *via* adduct **357**; for which the active peracid species (**356**) is initially generated by radical induced oxidation of the aldehyde (**355**) with O₂ (Scheme 167).⁴⁰⁹ Under such conditions, greater quantities of the acid (**358**) are formed relative to the formate ester (**359**).⁴⁰⁹ Thus, it was considered that under the oxidative reaction conditions, species **353** and **354** were formed primarily from reaction of aldehyde **341** with *m*CPBA, which is also consistent with the product ratios observed.⁴⁰⁹



Scheme 167. Mechanism for the molecular oxygen promoted oxidation of aldehyde **355**.⁴⁰⁹

In some instances a negligible peak was also observed at 10.03 ppm, which may be attributed to benzaldehyde arising from hydrolysis of the formate ester (**354**).⁴¹⁴ Such degradation is not unprecedented, as Ahmad *et al.* reported that keto acid **351** can be formed in 56% yield *via* hydrolysis of formate ester intermediate **350**, as shown previously in Scheme 165.^{242,411} It should be noted that many of the species formed may be particularly unstable and/or susceptible to hydrolysis.

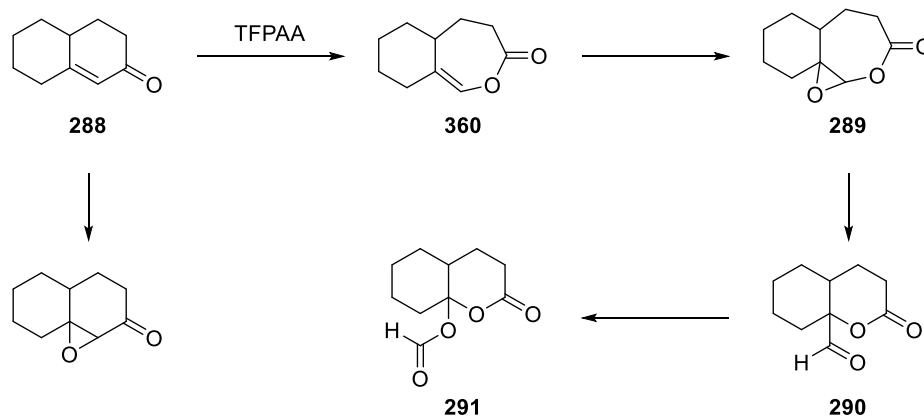
This unusual sequence of transformations has therefore been fully characterised, as summarised in Scheme 168. (*E*)-4-Phenyl-3-buten-2-one **336** may initially undergo Baeyer-Villiger oxidation with *m*CPBA to afford the desired vinyl ester **337** or undergo competitive epoxidation to form epoxy ketone **338**. The vinyl ester **337** may subsequently undergo epoxidation to give epoxy ester **339**, which may participate in acid catalysed intramolecular cyclisation and rearrangement to generate α -acetoxy aldehyde **341**. This newly generated carbonyl moiety is highly susceptible to Baeyer-Villiger oxidation by *m*CPBA; forming either the carboxylic acid **353** or formate ester **354** depending on which group migrates preferentially.



Scheme 168. Proposed sequence of transformations for the formation of the observed by-products.

For this system, conversions were determined by analysis of the ^1H NMR spectra obtained in deuterated chloroform for the crude reaction mixtures post aqueous work-up. Specifically, the ratio of species present was determined by comparison of the integrals for the peaks at 4.01, 5.56, 5.98, 6.05, 6.39, 6.73 and 7.76 ppm attributable to epoxy ketone **338**, epoxy ester **339**, carboxylic acid **353**, aldehyde **341**, vinyl ester **337**, α,β -unsaturated ketone **336** and formate ester **354** respectively.

A similar series of transformations have previously been reported for the oxidation of α,β -unsaturated ketones, confirming the validity of the proposed sequence (Scheme 169). For instance, the oxidation of $\Delta^{1(9)}$ -octalone-2 (**288**) with TFPAA published by DeBoer *et al.* proceeds *via* consecutive Baeyer-Villiger oxidation to form enol lactone intermediate **360**, epoxidation to epoxy lactone **289**, acid catalysed rearrangement to generate aldehyde lactone **290** and finally a further Baeyer-Villiger oxidation to afford formate species **291**.³⁶² Interestingly, in this instance performing the reaction with 2 equivalents of *m*CPBA provided exclusively epoxy ester **289**, as the less acidic *m*CBA by-product did not promote rearrangement in this case.³⁶²



Scheme 169. Series of transformations proposed for the TFPAA oxidation of 288 analogous to those observed for the *m*CPBA oxidation of 336.³⁶²

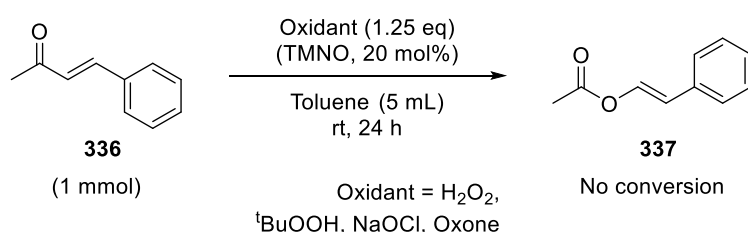
2.3.3 Development of conditions for the *N*-oxide promoted Baeyer-Villiger oxidation

As the reactions detailed in Table 4 progressed, a large quantity of white solid was found to suddenly precipitate from solution. It is noteworthy that this precipitation event occurred more rapidly within the catalysed system; for which the solid was isolated by filtration, air dried and then analysed by ¹H NMR spectroscopy. From the distinctive aromatic resonances within the ¹H NMR spectrum, it was deduced that the solid was comprised primarily of the *meta*-chlorobenzoic acid (*m*CBA) by-product.⁴¹⁵ This acidic species may be responsible for promoting the observed cyclisation and rearrangement of epoxy ester **339** into aldehyde **341**. Due to the loss of homogeneity of the reaction mixture upon precipitation, subsequent oxidations were performed with vigorous stirring to ensure consistent agitation was achieved.

Several work-up procedures suitable for removing the *m*CBA by-product as well as any residual and potentially explosive *m*CPBA were explored.⁴⁰¹ To circumvent the use of water, several solid bases, buffers and sacrificial species capable of being oxidised were added to quench the reaction, including: sodium carbonate, sodium phosphate, sodium thiosulfate, sodium sulphite, cyclohexene and triethylamine. Unfortunately, such methods were either not effective at removing the *m*CPBA/*m*CBA or resulted in degradation and/or removal of the unstable by-products (in particular epoxide **339**, aldehyde **341** and acid **353**). Loss of material appeared to be minimised when performing a sodium bicarbonate wash or upon addition of solid sodium bicarbonate or activated charcoal (Darco®),⁴¹⁶ with comparable product ratios observed in all cases. As the sodium bicarbonate wash was most effective at removing the *m*CPBA/*m*CBA, this work-up continued to be applied for subsequent reactions, with sufficient quantities added to ensure that all of the *m*CBA precipitate had dissolved. Nevertheless, solid sodium bicarbonate and activated charcoal (Darco®) are considered viable alternatives. It should be noted that quoted

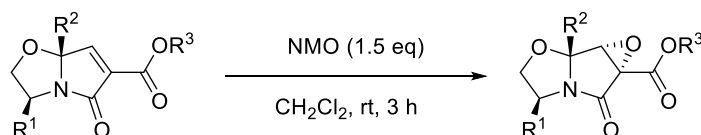
product ratios were considered semi-quantitative due to the inherent instability and potential water solubility of the products.

As *m*CPBA was found to be particularly active in promoting not only the desired Baeyer-Villiger oxidation but also several side reactions, numerous commercially available oxidants with a lower oxidising ability were then explored (Scheme 170). Under the aforementioned conditions, oxidations with H₂O₂ (50 wt% in water), ^tBuOOH (5M in decane), NaOCl (10% in water) and Oxone[®] (2KHSO₅•KHSO₄•K₂SO₄) were performed. However, in all cases no reaction was observed after 24 hours and only starting material was returned, even in the presence of trimethylamine *N*-oxide.



Scheme 170. Screen of potential oxidants for the Baeyer-Villiger oxidation of (*E*)-4-phenyl-3-buten-2-one (336).

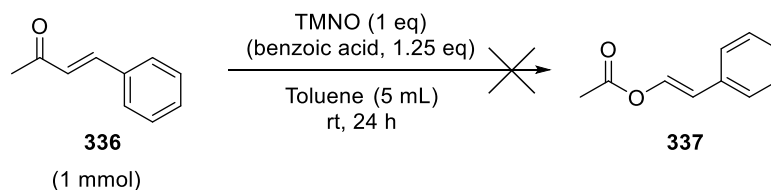
Due to the intrinsically weak and labile N→O bond,^{1,7} *N*-oxides have found application as oxidants within a wide variety of transformations. Notably, they have been utilised for the oxidation of α,β-unsaturated ketones to afford the corresponding epoxides (Scheme 171) and in the hydroxylation of aryl boronic acids and boronate esters, as described in Chapter 1.^{71,81}



Scheme 171. NMO as an organic oxidant for the synthesis of epoxides from α,β-unsaturated ketones.⁷¹

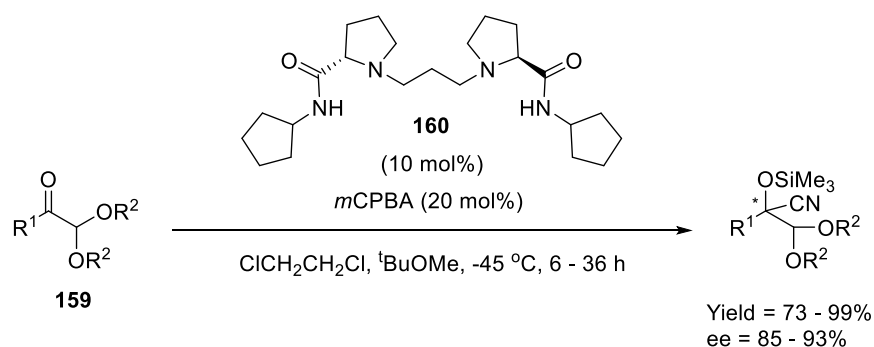
To ensure that trimethylamine *N*-oxide was not acting as a stoichiometric oxidant for the Baeyer-Villiger oxidation or promoting the formation of epoxides **338** and **339**, the reaction was repeated in the absence of *m*CPBA using 1 equivalent of trimethylamine *N*-oxide (Scheme 172). Crucially, no reaction was observed under these conditions or when the reaction was repeated in the presence of benzoic acid to mimic the acidic reaction conditions encountered using *m*CPBA. Accordingly, it may be concluded that the role of the TMNO is to solely catalyse the reaction and that the inserted oxygen originates from the *m*CPBA oxidant. Additionally, as *N*-oxides are

synthesized in high yield using organic peracids,⁶ it is unlikely that the *N*-oxide is acting as a co-oxidant within the reaction to regenerate the *m*CPBA from the carboxylic acid by-product.



Scheme 172. Examining the ability of TMNO to function as an oxidant for the Baeyer-Villiger oxidation of (*E*)-4-phenyl-3-buten-2-one (336).

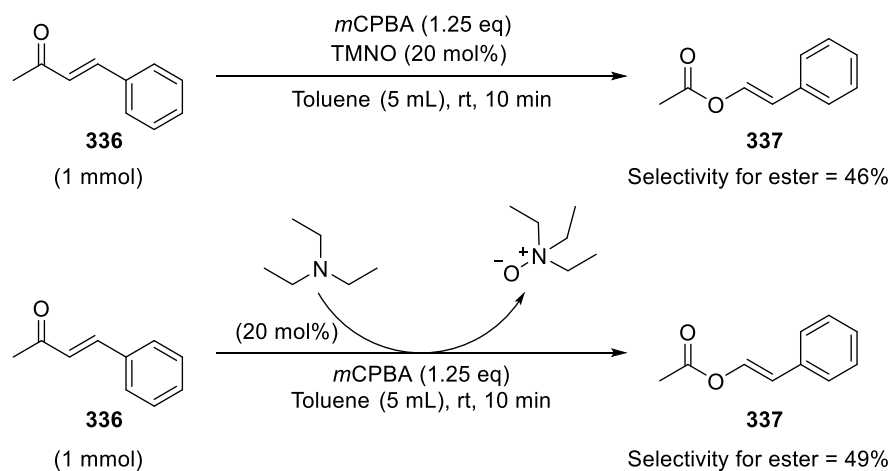
N-oxides are frequently prepared from the oxidation of the corresponding tertiary amine with *m*CPBA.⁶ Therefore, due to the oxidative reaction conditions, the potential for *in situ* generation of the catalytically active *N*-oxide species from the parent amine was investigated. A similar approach was successfully implemented by Feng and co-workers within the asymmetric cyanosilylation of α,α -dialkoxy ketones **159**; for which the *N,N'*-dioxide catalyst was generated *in situ* by oxidation of the parent tertiary amine (**160**) with *m*CPBA (Scheme 173).¹⁷⁵



Scheme 173. *In situ* formation of the catalytically active *N,N'*-dioxide from amine **160** within the asymmetric cyanosilylation of α,α -dialkoxy ketones **159**.¹⁷⁵

Initial studies were conducted to assess the ability of triethylamine to promote a selective Baeyer-Villiger oxidation. Although the initial rate appears unaffected by the catalysts, it was determined that comparable conversion and selectivity could be achieved using the amine (Table 5, entry 3) relative to that obtained for the structurally similar *N*-oxide (Table 5, entry 2). Excitingly, this implies that amines may successfully promote the Baeyer-Villiger oxidation of vinyl esters, presumably *via* the formation of the catalytically active *N*-oxide *in situ*. Due to the wide range of commercially available amines relative to *N*-oxides, this finding allows for the scope of potential catalysts to be greatly increased.

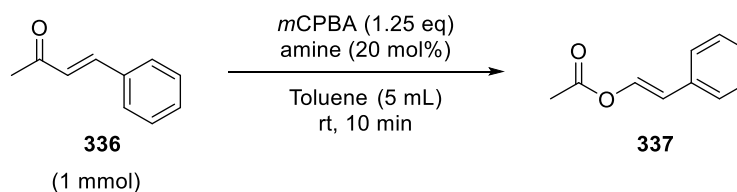
Table 5. Examining the potential for generating the *N*-oxide catalyst *in situ* from the corresponding amine.



Entry	Catalyst	Ket. 336	Ester 337	Epox. 339	Ald. 341	Acid 353	Form. 354	Epox. 338
1	-	32	37	21	1	3	2	4
2	TMNO	29	46	21	1	1	-	2
3	Et ₃ N	33	49	16	-	-	-	2

Product ratios were determined by ¹H NMR spectroscopic analysis.

Subsequently, a range of aromatic and aliphatic based amines were screened to assess their relative catalytic activity (Table 6). As shown in Table 6, 4-(dimethylamino)pyridine (DMAP) was found to achieve the highest selectivity for vinyl ester **337**; promoting the desired reaction whilst also minimising formation of the undesired over-oxidation products (Table 6, entry 8). Interestingly, DMAP was found to afford far superior results relative to pyridine (Table 6, entry 7 vs 8). This may be rationalised by the relative ability of the *in situ* generated *N*-oxide to function as a hydrogen bond acceptor. It is due to inductive and resonance stabilisation by the conjugated, strongly electron donating dimethylamino group that DMAP is more nucleophilic, basic (*cf.* pK_{aH} : py = 5.23, DMAP = 9.58)^{392,393} and a stronger hydrogen bond acceptor than pyridine (*cf.* pK_{BHX} : py = 1.86, DMAP = 2.80).^{393,394} Whilst hydrogen bond basicity (pK_{BHX}) often cannot be directly correlated with basicity (pK_{aH}), this is possible for structurally related families of compounds.^{393,394} Therefore, it may be inferred that DMAP *N*-oxide, which is more basic than pyridine *N*-oxide (*cf.* pK_{aH} : PNO = 0.79, DMAPO = 3.88),^{392,417} is also a stronger hydrogen bond acceptor, which may explain the observed activity difference of these two species. Interestingly, applying preformed pyridine *N*-oxide within this methodology gave similarly poor results to the parent amine; indicating that the discrepancy in activity between DMAP and pyridine is not due to the rate of *N*-oxide formation.

Table 6. Screen of amine pre-catalysts for the Baeyer-Villiger oxidation of (*E*)-4-phenyl-3-buten-2-one (**336**) with *m*CPBA.


Entry	Catalyst	Ket. 336	Ester 337	Epox. 339	Ald. 341	Acid 353	Form. 354	Epox. 338
1	-	32	33	24	1	5	2	3
2	Triethylamine	41	44	14	-	-	-	1
3	DIPEA	33	42	15	4	3	1	2
4	<i>N</i> -Methylpyrrolidine	36	42	6	11	2	1	2
5	<i>N</i> -Methylpiperidine	33	48	6	10	1	-	2
6	<i>N</i> -Methylmorpholine	32	48	8	8	1	1	2
7	Pyridine	47	35	7	6	3	-	2
8	DMAP	27	62	8	-	1	-	2

Product ratios were determined by ^1H NMR spectroscopic analysis.

Following the success of DMAP, more elaborate 4-aminopyridine derivatives were explored. It was considered that greater electron density on the heterocyclic portion of the corresponding *N*-oxide may further increase the contribution of resonance forms A-E to the resonance hybrid, which would be conducive to increased basicity and stronger hydrogen bonding interactions (Figure 29).^{3,418} Such 4-aminopyridine derivatives are commonly employed as nucleophilic catalysts within esterification and acylation reactions, with the relative activity of these species determined as follows: 4-pyrrolidino > 4-dimethylamino > 4-piperidino > 4-morpholino (Figure 30).^{419,420} Importantly, this series parallels the relative basicity of the species.⁴²¹⁻⁴²³ Specifically, the enhanced induction and therefore electron density on the heterocyclic ring of the 4-pyrrolidino derivative, which makes it more reactive than DMAP, is a result of the restricted geometry of the nitrogen within the pyrrolidine fragment, which serves to improve orbital overlap with the aromatic system.⁴¹⁸⁻⁴²⁰ Therefore, 4-(pyrrolidin-1-yl)pyridine **361** and 4-(piperidin-1-yl)pyridine **362** were identified as species of interest.

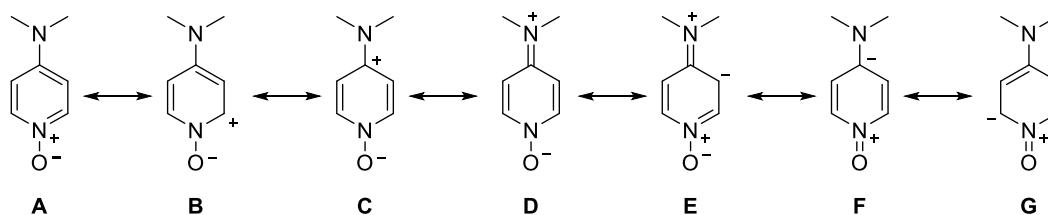


Figure 29. Resonance structures of 4-dimethylaminopyridine *N*-oxide.³

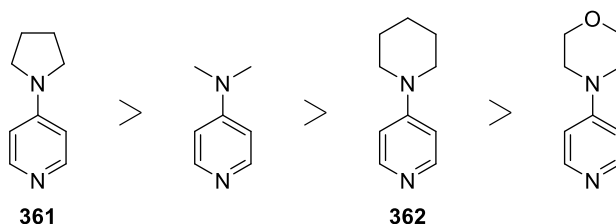
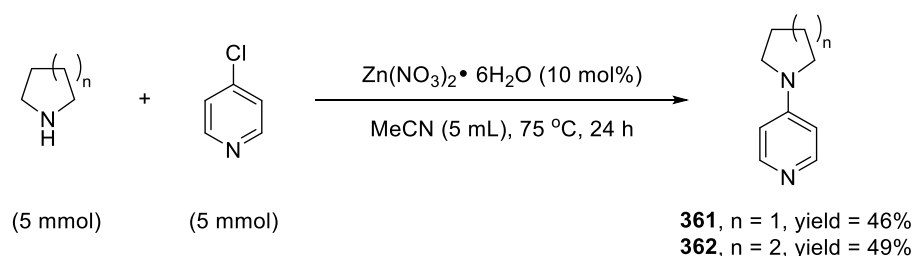


Figure 30. Relative nucleophilicity of 4-aminopyridine derivatives.⁴¹⁹

According to a procedure developed within the group, 4-(pyrrolidin-1-yl)pyridine **361** and 4-(piperidin-1-yl)pyridine **362** were prepared *via* the $\text{Zn}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ mediated amination of 4-chloropyridine with the appropriate cyclic amine, either pyrrolidine or piperidine, in moderate yield (46% and 49% respectively) (Scheme 174).⁴²⁴ Specifically, the reaction was conducted at 75 °C for 24 hours and the crude products were purified by flash column chromatography.⁴²⁴



Scheme 174. Synthesis of **361** and **362** *via* the $\text{Zn}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ mediated amination of 4-chloropyridine with the appropriate cyclic amine.⁴²⁴

As anticipated, 4-(pyrrolidin-1-yl)pyridine performed marginally better than DMAP (Table 7, entry 2), whilst 4-(piperidin-1-yl)pyridine gave slightly poorer selectivity for vinyl ester **337** (Table 7, entry 3). However, this latter catalyst appeared to be more effective at preventing over-oxidation. Whilst these cyclic 4-aminopyridine derivatives showed a slight improvement on the results obtained when using the acyclic species, due to being inexpensive and commercially available DMAP was carried forward for further optimisation studies. Although 4-aminopyridines have been reported to function as nucleophilic catalysts, the success of non-nucleophilic bases, such as DBU and DBN, within the oxidation suggests that the catalyst is assuming an alternative role in this instance (Table 7, entries 4 and 5).

Table 7. Exploring the potential of DMAP derivatives and non-nucleophilic bases to promote the Baeyer-Villiger oxidation of (*E*)-4-phenyl-3-buten-2-one (336**) with *m*CPBA.**

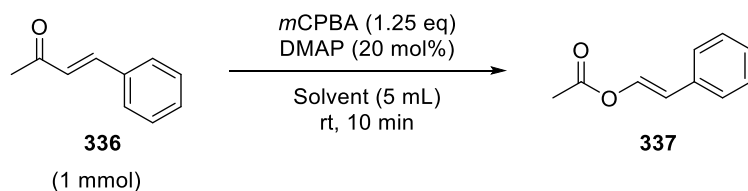

Entry	Catalyst	Ket. 336	Ester 337	Epox. 339	Ald. 341	Acid 353	Form. 354	Epox. 338
1	DMAP	27	62	8	-	1	-	2
2	361	22	69	5	2	-	-	2
3	362	36	60	1	2	-	-	1
4	DBU	25	52	13	5	2	1	2
5	DBN	26	51	19	1	1	-	2
6	DABCO	49	36	5	6	2	-	2

Product ratios were determined by ^1H NMR spectroscopic analysis.

Having identified a suitable amine catalyst, solvent effects were explored (Table 8). The solvents examined encompass a wide spectrum of polarities and include both protic and aprotic media. As anticipated, non-polar aprotic solvents, such as dichloromethane, toluene and hexane, gave far superior conversions to vinyl ester **337** (Table 8, entries 7, 8 and 10). Such aprotic solvents are known to promote short, strong hydrogen bonds between reagents, as they cannot participate in competitive hydrogen bonding interactions themselves, which would otherwise disrupt the desired proton transfer pathways.^{425,426} Additionally, the lower the solvent polarity, the stronger the hydrogen bond, which correlates with the observed trend in selectivity. Therefore, these findings are indicative of important hydrogen bonding interactions within the rate-determining step. In support of this, acetonitrile and methanol, which exhibit similar dielectric constants (*cf.* acetonitrile: 37.5 and methanol: 32.6) and are therefore of comparable polarity, gave disparate results (Table 8, entries 1 and 4).^{321,427} Whilst acetonitrile is an aprotic solvent, methanol can function as both a hydrogen bond donor and acceptor; with this property most likely accounting for the lower conversion observed. Such solvent effects are consistent with the *N*-oxide catalyst promoting concerted proton transfer within the rate-determining step. Furthermore, the carboxylic acid present in peracid oxidations has been reported to function as a proton relay catalyst for reactions performed in such non-polar solvents; avoiding the high energy 4-membered transition state within the addition step and also potentially promoting the migration step.^{230,233,280,281,292,296,327} Due to the sparing solubility of *m*CPBA in hexane and the regulatory

restrictions associated with both hexane and dichloromethane, toluene was identified as the most suitable solvent.^{428,429} It is noteworthy that with seemingly less active batches of *m*CPBA, toluene was found to be superior to hexane and produced more consistent results.

Table 8. Solvent screen for the Baeyer-Villiger oxidation of (*E*)-4-phenyl-3-buten-2-one (**336**) with *m*CPBA.



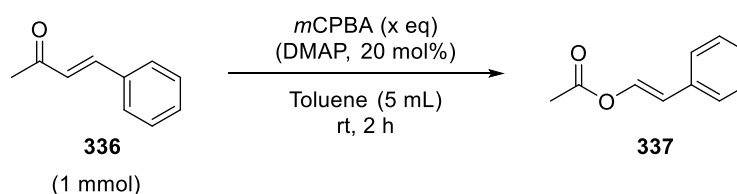
Entry	Solvent	Ket. 336	Ester 337	Epox. 339	Ald. 341	Acid 353	Form. 354	Epox. 338
1	MeOH	82	13	-	1	1	-	3
2	EtOH	83	13	-	2	-	-	2
3	Trifluoroethanol	57	36	4	-	1	-	2
4	MeCN	38	53	7	-	-	-	2
5	EtOAc	52	34	9	2	1	-	2
6	THF	55	38	5	1	-	-	1
7	CH ₂ Cl ₂	23	66	9	-	-	-	2
8	PhMe	22	66	10	1	-	-	1
9	Trifluorotoluene	26	61	11	-	-	-	2
10	Hexane	19	74	5	1	-	-	1

Product ratios were determined by ¹H NMR spectroscopic analysis.

In an attempt to increase consumption of the α,β-unsaturated ketone the reactions were performed with increasing amounts of *m*CPBA for an extended reaction time of 2 hours. Although the oxidations are extremely rapid initially (Table 8, entry 8, 10 minutes), the reaction appears to stall; with similar levels of starting material **336** remaining after 2 hours using 1.25 equivalents of *m*CPBA (Table 9, entry 2). This finding may potentially be attributed to the precipitation event described previously. As determined by analysis of the ¹H NMR spectrum, the collected solid was found to contain *m*CBA by-product and small quantities of DMAP or a related species [δ_{H} = 8.46 (2H, d, J = 7.1 Hz), 6.68 (2H, d, J = 6.7 Hz), 3.18 (6H, s)]. Crucially, both of these species are thought to promote the desired Baeyer-Villiger oxidation and therefore it may be inferred that the activation energy for reaction is prohibitively high in their absence.^{280,281,296} Alternatively, the observed drop off in reaction rate may be accounted for by base promoted decomposition of the

organic peracid, which has been reported previously under aqueous alkaline conditions.^{228,430} As may be expected, with higher quantities of *m*CPBA oxidant greater consumption of the starting material could be achieved (Table 9, entries 3-8). However, this was accompanied by a decrease in selectivity for the vinyl ester **337** due to increasing levels of undesired, competitive over-oxidation. Nevertheless, the *N*-oxide universally gave better control over the selectivity of the reaction for **337** relative to the background; promoting only the desired oxidation. From this study 1.5 equivalents of *m*CPBA was regarded as the optimum for achieving high consumption of the starting material, whilst preventing excessive degradation of the vinyl ester **337**. Interestingly, dosing in additional reagents (*m*CPBA and DMAP) as well as performing a dropwise addition of the *m*CPBA, in an attempt to overcome the aforementioned problems, gave little improvement.

Table 9. Examining the conversion and product selectivity for the Baeyer-Villiger oxidation of (*E*)-4-phenyl-3-buten-2-one (336) with varying quantities of *m*CPBA.



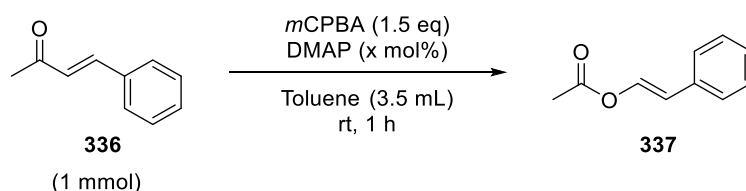
Entry	Amount <i>m</i> CPBA (equiv.)	Ket. 336	Ester 337	Epox. 339	Ald. 341	Acid 353	Form. 354	Epox. 338
1	1.25	39	28	11	11	5	3	3
2	1.25, DMAP	21	71	7	-	-	-	1
3	1.5	23	34	27	3	4	4	5
4	1.5, DMAP	6	79	12	1	-	-	2
5	2.0	15	27	28	6	11	9	4
6	2.0, DMAP	-	68	22	6	2	-	2
7	2.5	11	15	-	22	20	27	5
8	2.5, DMAP	-	47	18	25	8	-	2

Product ratios were determined by ¹H NMR spectroscopic analysis.

Irrespective of the reaction concentration (1-5 mL toluene), analogous results were achieved. Due to the loss of homogeneity during the reaction and the sparing solubility of the peracid:acid reagent, 3.5 mL of toluene was considered optimal, with such dilute conditions also potentially allowing for better control of any exotherm encountered upon scale-up. However, for less reactive substrates or where minimum solvent usage is advantageous, a more concentrated reaction may be conducted without loss of selectivity.

Unexpectedly, as the catalyst loading was increased from 5 to 50 mol% the extent of both the desired Baeyer-Villiger oxidation and competitive oxidation events were reduced, with these factors influencing the overall selectivity for vinyl ester **337** in opposing manners (Table 10, entries 2-6). Accordingly, it was determined that 20 mol% DMAP achieved the best balance of these factors, whilst also ensuring catalyst loading was kept to a minimum. It was considered that the reduced extent of reaction with higher catalyst loading may be an artefact of the *m*CPBA being consumed to generate the *N*-oxide catalyst. However, the same trend was observed when employing preformed DMAPO, with similar selectivity for **337** achieved using 20 mol% of this species (Table 10, entry 4 and 7). Alternatively, the reduced reaction rate at higher catalyst loadings may potentially be attributed to undesirable hydrogen bonding interactions. Aromatic *N*-oxides are known to readily form hydrogen bonded aggregates both with themselves and other hydrogen bond donors, such as the peracid and carboxylic acid present.^{395-399,431} Such aggregation may consequently prevent these reagents participating in the desired reaction, which may account for the observed trend, as this phenomenon would be more prevalent at higher concentrations. Unfortunately, the extent of the desired Baeyer-Villiger oxidation of **336** could not be significantly improved by extending the reaction time. As previously mentioned the reaction appears to stall, with similar selectivity (within 3%) achieved after 1, 2 and 4 hours for both the catalysed and uncatalysed systems.

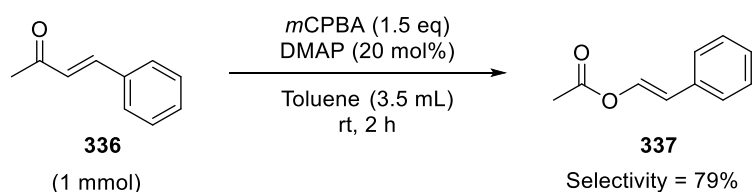
Table 10. Examining the conversion and product selectivity for the Baeyer-Villiger oxidation of (*E*)-4-phenyl-3-buten-2-one (336**) with varying quantities of DMAP.**



Entry	Catalyst loading (mol%)	Ket. 336	Ester 337	Epox. 339	Ald. 341	Acid 353	Form. 354	Epox. 338
1	0	31	27	6	18	9	5	4
2	5	1	72	13	11	1	-	2
3	10	4	75	17	1	1	-	2
4	20	10	75	11	2	-	-	2
5	30	14	74	10	-	-	-	2
6	50	37	55	6	-	-	-	2
7 ^a	20	12	71	16	-	-	-	1

Product ratios were determined by ¹H NMR spectroscopic analysis. ^aReaction performed with preformed DMAPO.

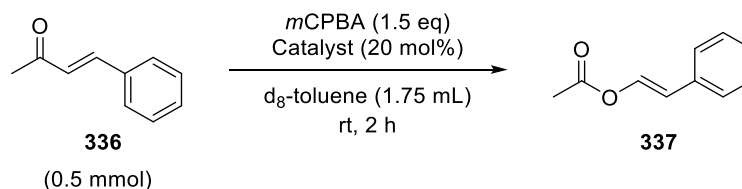
Therefore, readily available DMAP has been found to promote the Baeyer-Villiger oxidation of (*E*)-4-phenyl-3-buten-2-one (**336**) in relatively low catalyst loading (20 mol%), with greatly improved selectivity and reaction rate relative to the uncatalysed counterpart achieved. Pleasingly, with only a small excess of *m*CPBA the oxidation is particularly rapid and a reaction time of two hours was deemed optimal to allow for the method to be extended to more deactivated substrates. The optimised conditions are summarised in Scheme 175.



Scheme 175. Optimised reaction conditions for the Baeyer-Villiger oxidation of (*E*)-4-phenyl-3-buten-2-one (**336**).

Many of the species generated from the *m*CPBA oxidation of (*E*)-4-phenyl-3-buten-2-one (**336**) are potentially unstable, susceptible to hydrolysis and/or water soluble. As previously mentioned, the quoted ratios were therefore considered semi-quantitative; effectively providing a method for establishing the relative selectivity of each reaction. To further substantiate the validity of these results, the oxidations were repeated in deuterated toluene under the optimised reaction conditions. Crucially, this allowed for the crude reaction mixture to be directly analysed by ^1H NMR spectroscopy without the need to conduct a work-up, which may otherwise degrade or remove the products; altering the conversions. Pleasingly, comparable selectivity was observed for vinyl ester **337** under all conditions tested relative to reactions that had been analysed post-aqueous work-up; albeit with slightly greater quantities of epoxy ester **339** observed (Table 11). The greatly improved reaction profile and selectivity afforded in the presence of DMAP is clearly highlighted in the ^1H NMR spectra displayed in Figure 31 and Figure 32 for the uncatalysed and catalysed reactions respectively, which were obtained after 2 hours.

Table 11. Product distributions determined from *in situ* ^1H NMR studies performed in deuterated toluene.



Entry	Catalyst	Ket. 336	Ester 337	Epox. 339	Ald. 341	Acid 353	Form. 354	Epox. 338
1	-	35	31	25	1	1	4	3

2	DMAP	4	75	19	-	-	-	2
3	DMAPO	11	73	15	-	-	-	1

Product ratios were determined by ^1H NMR spectroscopic analysis.

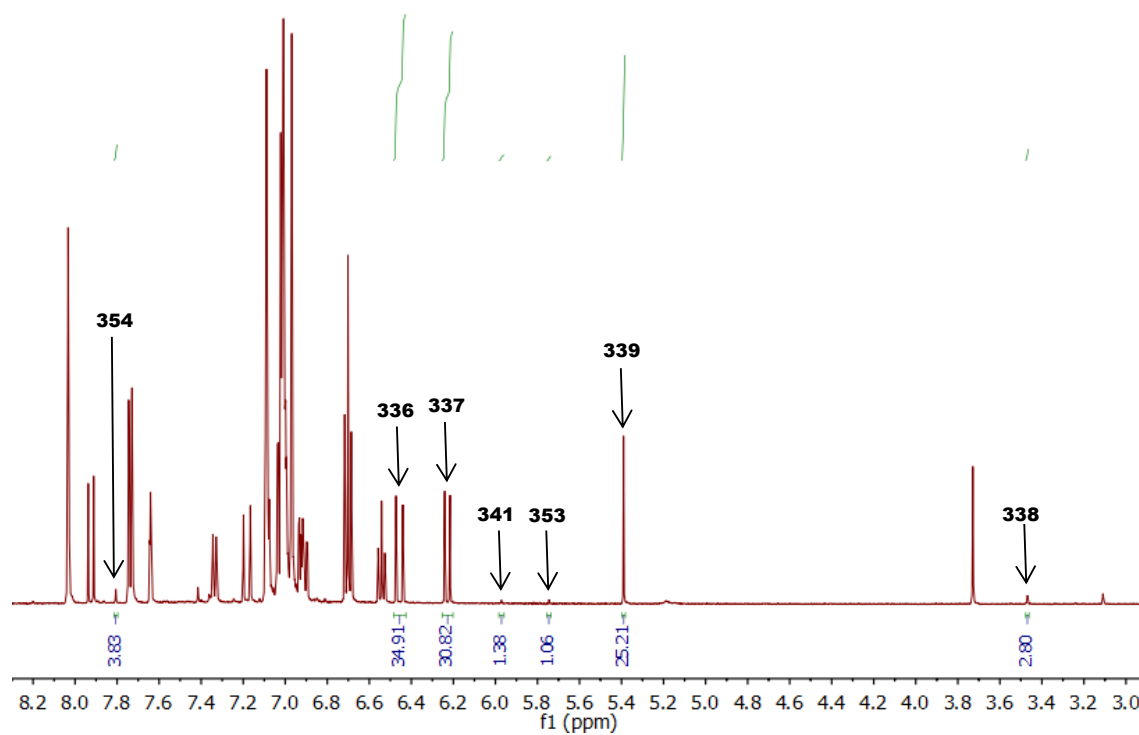


Figure 31. 500 MHz ^1H NMR spectrum obtained in deuterated toluene for the crude uncatalysed reaction mixture.

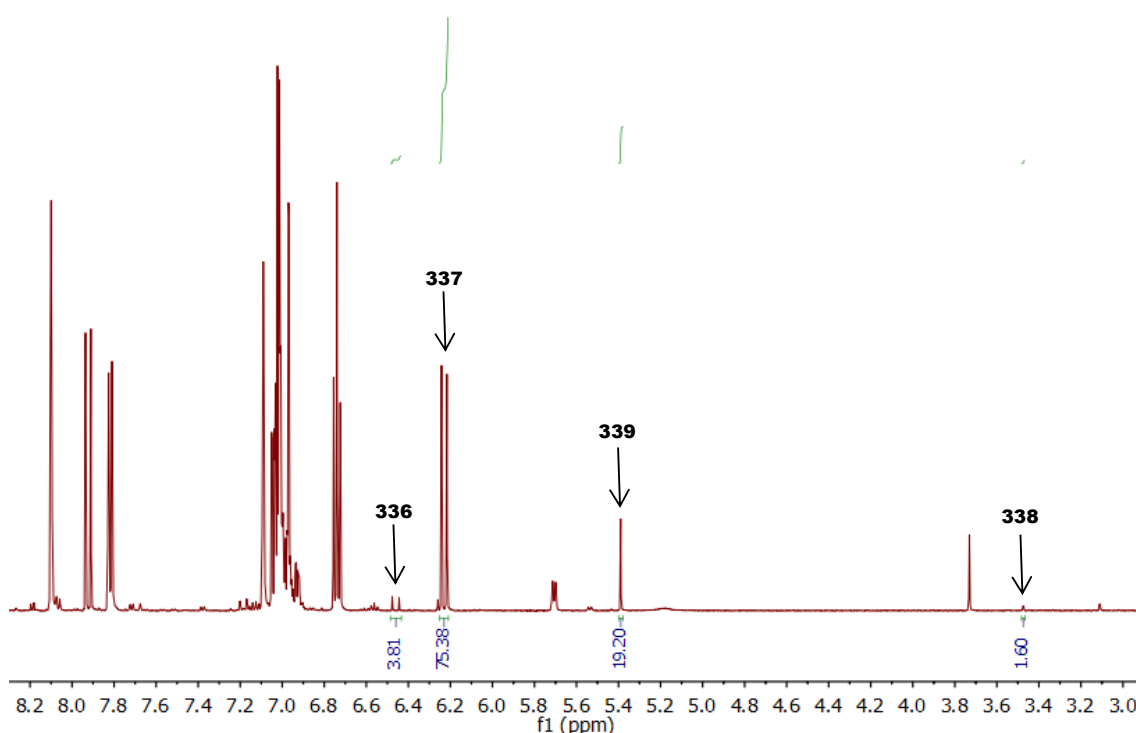


Figure 32. 500 MHz ^1H NMR spectrum obtained in deuterated toluene for the oxidation of (*E*)-4-phenyl-3-buten-2-one (**336**) performed in the presence of DMAP.

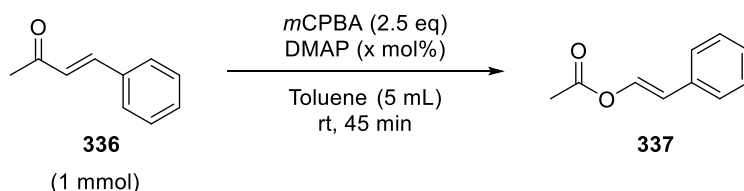
It is noteworthy that a discrepancy in activity was observed between different batches of *m*CPBA, which were consistently sourced from Sigma Aldrich (supplied in $\leq 77\%$ purity). Due to their inherent instability, organic peracids such as *m*CPBA are supplied as a mixture of the peracid, parent carboxylic acid and water.^{281,323,326} As weak acids promote the Baeyer-Villiger oxidation, the oxidant is essentially supplied in combination with a suitable catalyst.^{281,323} However, as a result of the preparative methods used to synthesize such oxidants, the amount of peracid oxidant and accompanying carboxylic acid may potentially vary between different batches.^{228,323,326} It is this variation in the composition of the active species that accounts for the difference in activity observed.^{228,294,323} It is unclear whether higher levels of the active oxidant (*m*CPBA) or general acid catalyst (*m*CBA) are responsible for the increased oxidising potential of some batches. The best result achieved under the optimised conditions provided 86% selectivity for vinyl ester **337**, with slightly reduced quantities of the over-oxidation products also observed.

The aforementioned optimisation screens were performed with a seemingly more active batch of the peracid:acid combination, with a slightly higher background rate and levels of over-oxidation observed. Nevertheless, selectivity for vinyl ester **337** was comparable ($<10\%$) across all batches of *m*CPBA. An iodometric titration was performed to determine the purity of one of the batches of *m*CPBA, which revealed the purity of this reagent was at the maximum of the expected range

(79%). Thus, based on the supplier's specifications, all reactions were performed assuming the *m*CPBA was of 77% purity. However, this does not take into consideration the amount of carboxylic acid present.

As an aside, the extent of the desired Baeyer-Villiger oxidation of **336** is known to increase with greater quantities of *m*CPBA oxidant, whilst higher catalyst loadings have been found to minimise degradation of vinyl ester **337**. Therefore, it was rationalised that the high levels of over-oxidation associated with employing greater quantities of *m*CPBA may be overcome by utilising a higher catalyst loading. It was hoped that this would allow for increased levels of starting material consumption as well as selectivity for the desired oxidation product **337**. The results detailed in Table 12 demonstrate that the Baeyer-Villiger oxidation of **336** proceeds to completion with 2.5 equivalents of *m*CPBA after 45 minutes. Undesired epoxidation of the vinyl ester product (**337**) and subsequent transformations were successfully minimised by increasing the quantity of DMAP employed, with an impressive 91% selectivity for **337** achieved in the presence of 50 mol% DMAP. However, these conditions were not pursued any further, as they rendered the process extremely wasteful, with a high resource demand.

Table 12. Examining the conversion and product selectivity for the Baeyer-Villiger oxidation of (*E*)-4-phenyl-3-buten-2-one (336**) with a greater excess of *m*CPBA and higher loading of DMAP.**



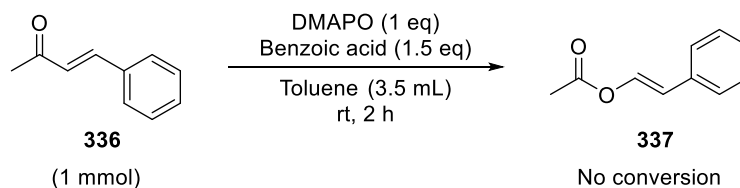
Entry	Catalyst loading (mol%)	Ket. 336	Ester 337	Epox. 339	Ald. 341	Acid 353	Form. 354	Epox. 338
1	20	-	65	28	2	3	-	2
2	30	-	71	25	2	1	-	1
3	50	-	91	7	-	-	-	2

Product ratios were determined by ¹H NMR spectroscopic analysis.

2.3.4 Mechanistic studies

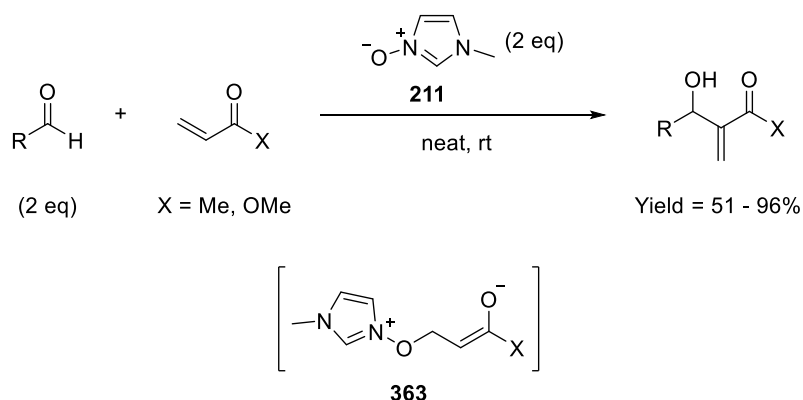
Studies were then focussed on elucidating the role of the *N*-oxide within the reaction mechanism. During the aforementioned reaction optimisation studies, it was established that the *N*-oxide does not function as an oxidant. To confirm that this result is applicable to DMAPO, the parent substrate was treated with this aromatic *N*-oxide in the presence of benzoic acid (Scheme 176). Consistent with the original result, no oxidation of the α,β-unsaturated ketone was found to occur.

Additionally, the observed solvent effects and electronic requirements of the catalyst are consistent with the *N*-oxide facilitating concerted proton transfer in the rate determining step.



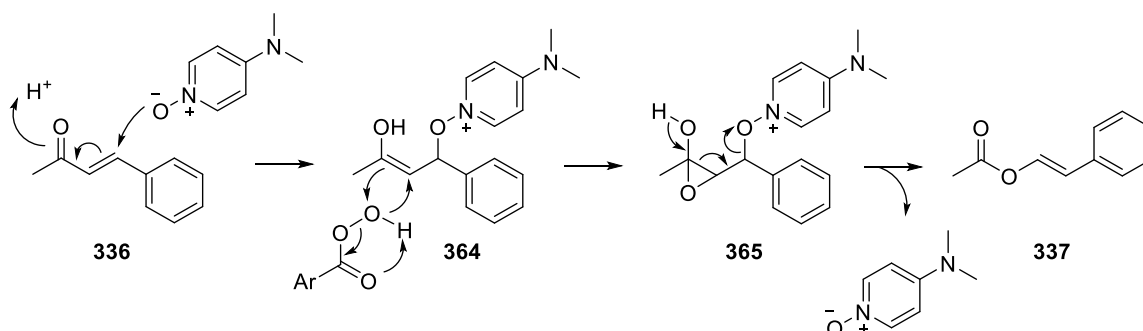
Scheme 176. Exploring the potential of DMAPO to function as an oxidant within the Baeyer-Villiger oxidation of (*E*)-4-phenyl-3-buten-2-one (**336**).

However, *N*-oxides have the capacity to function as nucleophilic catalysts and 1,4-conjugate addition of *N*-oxides to α,β -unsaturated ketones has been reported within the literature. For instance, Tsai *et al.* postulated that in the 1-methylimidazole 3-*N*-oxide (**211**) promoted Morita-Baylis-Hillman reaction the *N*-oxide adds in a 1,4-manner to the ketone, either methyl vinyl ketone or methyl acrylate, to generate the reactive enolate species **363**, as detailed in Scheme 177 (see Section 1.4.6).²⁰⁹

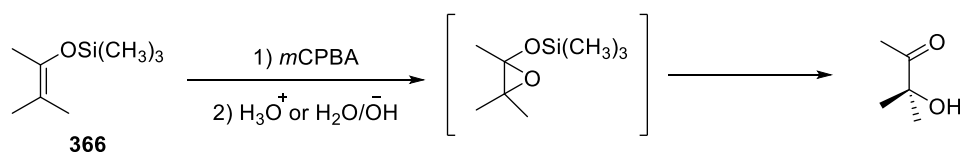


Scheme 177. Proposed 1,4-conjugate addition of 1-methylimidazole 3-*N*-oxide (**211**) to α,β -unsaturated ketones to form intermediate **363** as the first step of the MBH reaction.²⁰⁹

Therefore, a mechanism involving initial 1,4-conjugate addition of the *N*-oxide to the α,β -unsaturated ketone **336** to form enol **364**, was considered feasible (Scheme 178). Since literature precedent also exists for the epoxidation of related trimethylsilyl enol ethers **366** in the presence of *m*CPBA (Scheme 179),⁴³² it is plausible that enol intermediate **364** undergoes epoxidation (**365**) and subsequent rearrangement to afford the desired product **337** (Scheme 178).

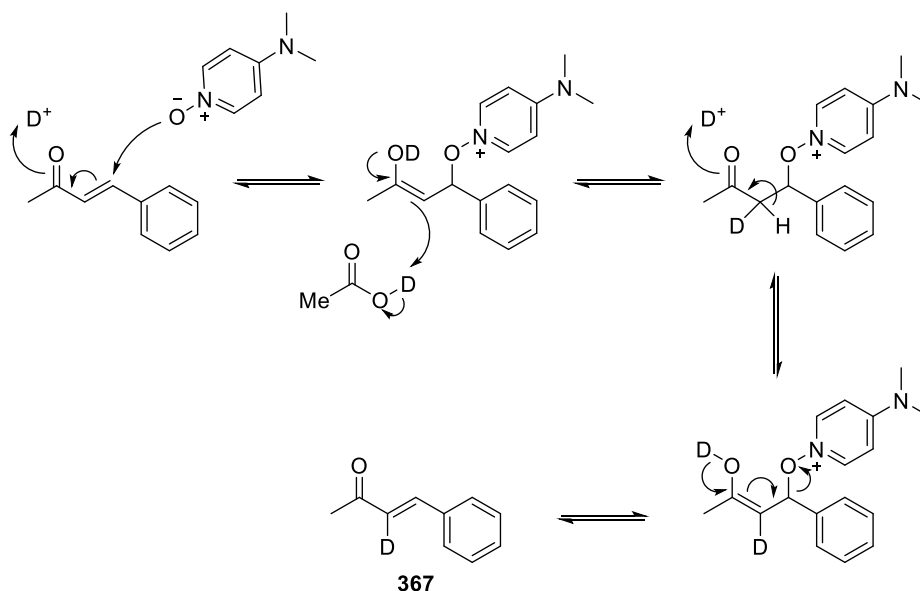


Scheme 178. Potential 1,4-conjugate addition pathway for the *N*-oxide promoted Baeyer-Villiger oxidation of **336**.



Scheme 179. α -Hydroxylation of silyl enol ethers using *m*CPBA.⁴³²

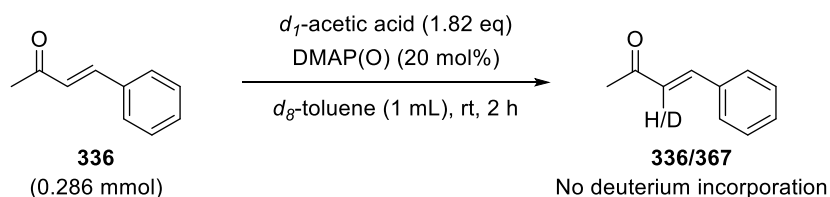
In an attempt to determine whether the *N*-oxide was functioning in this manner as a nucleophilic catalyst, a series of deuterium incorporation experiments was performed; initially using d_1 -acetic acid. It may be anticipated that deuterium would be incorporated into the α -vinylic position of the α,β -unsaturated ketone (**367**), according to the mechanism given in Scheme 180, if the reaction was proceeding *via* initial 1,4-conjugate addition (Scheme 178).



Scheme 180. Expected deuterium incorporation for a mechanism proceeding *via* initial 1,4-conjugate addition of the *N*-oxide.

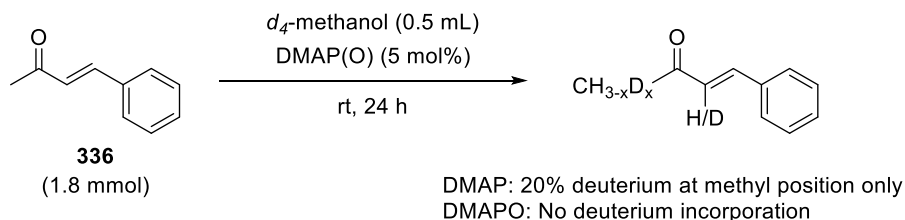
For this isotopic labelling study, *m*CPBA was substituted for deuterated acetic acid in order to mimic the reaction conditions and the resultant mixture was analysed by both ^1H and ^2H NMR

spectroscopy after 2 hours (Scheme 181). However, no deuterium incorporation was observed in the presence of DMAPO or the parent amine, DMAP, suggesting that 1,4-conjugate addition of the catalyst to the starting material is unlikely to be occurring in the initial reaction step.



Scheme 181. Deuterium labelling study conducted with d_1 -acetic acid.

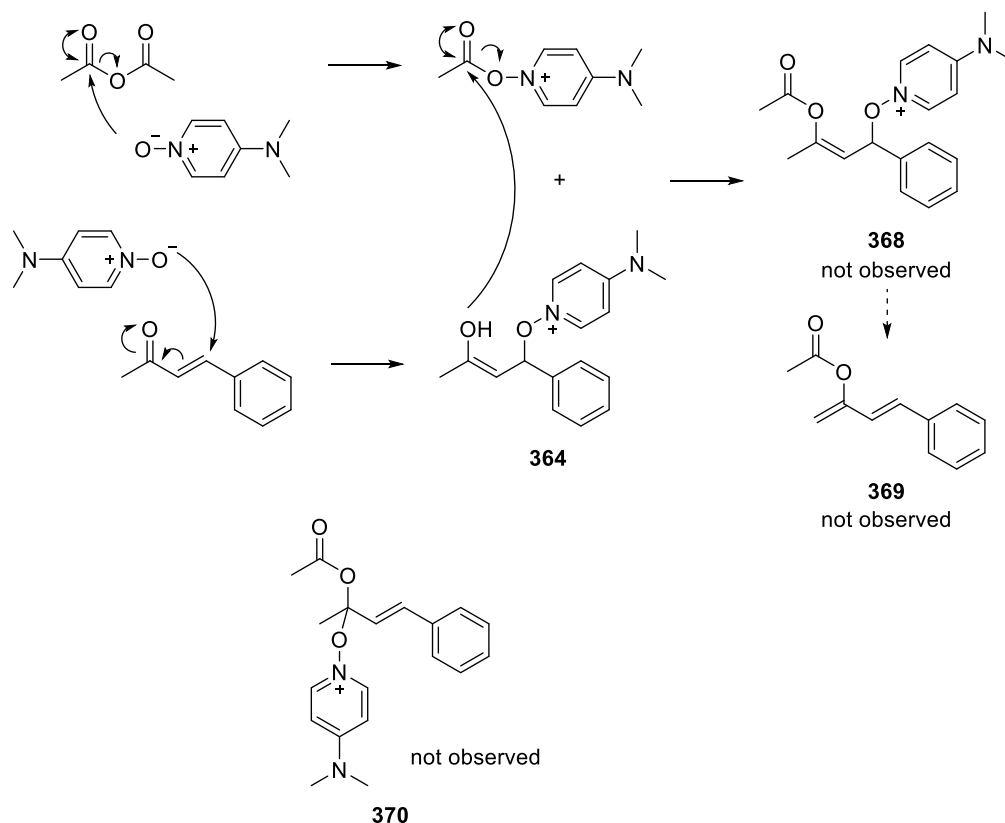
Similarly, no deuterium incorporation was observed at the α -vinyl position of **336** after exposure of this α,β -unsaturated ketone to the catalyst in d_4 -methanol for 24 hours (Scheme 182). For a mechanism proceeding *via* 1,4-conjugate addition, incorporation would again be expected. However, it is noteworthy that 20% deuterium incorporation was observed at the methyl position for the DMAP system, with a mixture of 4 methyl isotopologues produced (CH_3 , CH_2D , CHD_2 , CD_3), as determined by ^1H and ^2H NMR studies. Specifically, the presence of these species was determined from the 3 distinct signals in the ^2H NMR spectrum corresponding to the 3 deuterated isotopologues and the characteristic splitting patterns of the signals attributed to the protonated counterparts within the ^1H NMR spectrum. The level of deuterium incorporation was calculated by comparison of the integral for the methyl signals relative to those attributable to the {PhCH} fragment.



Scheme 182. Deuterium incorporation study conducted with d_4 -methanol.

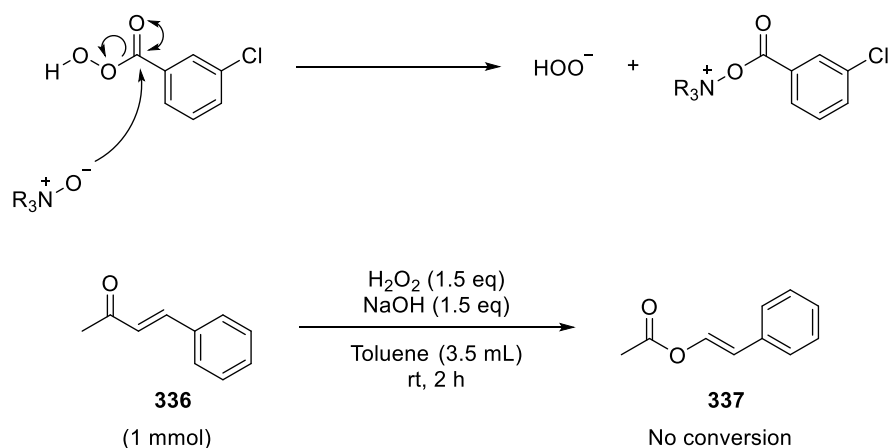
Furthermore, it was proposed that if an enol (**364**) was being formed as an intermediate within the Baeyer-Villiger oxidation then it might be possible to ‘trap out’ this species *via* acetylation with acetic anhydride (Scheme 183). DMAP and more recently DMAPO have been reported to be effective acylation catalysts, as highlighted earlier in sections 1.4.2 and 1.4.4. Therefore, substitution of *m*CPBA for acetic anhydride and performing the reaction in a slight excess of catalyst would be expected to generate species **368** and/or **369** if the oxidation was proceeding *via* initial 1,4-conjugate addition.^{201,205,433} However, no transformation was observed and just the starting material was recovered even in the presence of benzoic acid; providing further evidence against the pathway shown in Scheme 178. Additionally, 1,2-addition of the *N*-oxide could be

ruled out based on the absence of species **370**. Further supporting the lack of interaction, when the substrate and catalyst were combined in a 1:1 ratio, no shift was observed for the proton peaks attributed to DMAP/DMAPO or (*E*)-4-phenyl-3-buten-2-one **336** within the ^1H NMR spectra obtained in d_8 -toluene.



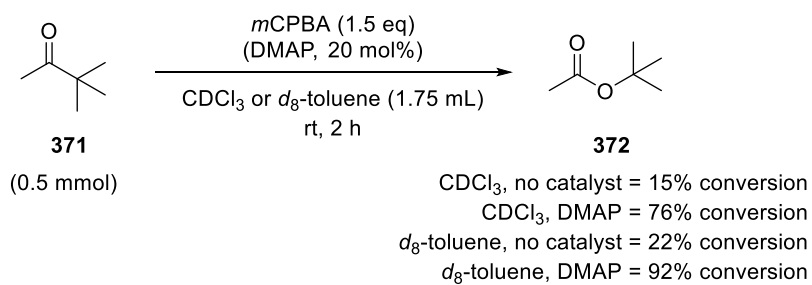
Scheme 183. Expected products from the DMAP(O) catalysed acylation of enol intermediate **364**.

Alternatively, it was considered that the *N*-oxide may be participating in 1,2-addition with the *m*CPBA, to generate a more nucleophilic peroxide mono-anion (^-OOH) oxidant (Scheme 184). In order to probe this mechanistic pathway, the hydrogen peroxide oxidation of (*E*)-4-phenyl-3-buten-2-one (**336**) was performed in the presence of sodium hydroxide. No reaction was observed; allowing for this hypothesis to be discounted.



Scheme 184. Examining the potential for peroxide mono-anion (OOH^-) to function as an oxidant.

To ascertain whether the alkene functionality was required for the *N*-oxide to promote the Baeyer-Villiger oxidation, the reaction of 3,3-dimethyl-2-butanone (**371**), a simple saturated ketone, was performed (Scheme 185). As the ketone (**371**) and corresponding ester product (**372**) are particularly volatile, applying the standard work-up procedure, which involves concentration of the reaction mixture *in vacuo*, was not considered viable, as it would result in large losses of material. Therefore, to circumvent this problem the reaction was conducted with stirring in d_8 -toluene to allow for direct analysis of the crude reaction mixture by ^1H NMR spectroscopy. After 2 hours the mixture was diluted with further d_8 -toluene, to ensure that all of the precipitate had dissolved, and an aliquot of the mixture was removed for analysis. Excitingly, DMAP was found to greatly accelerate the oxidation of 3,3-dimethyl-2-butanone (*cf.* 92% *vs* 22%); demonstrating that the alkene moiety is only a spectator within the desired Baeyer-Villiger oxidation and does not play a role in the observed catalysis. Additionally, this highlighted that the methodology was not just limited to enones and could be applied to a more diverse range of potential substrates. As may be anticipated, DMAP also exhibited a catalytic effect for the analogous oxidation performed in CDCl_3 ; albeit with slightly reduced conversions (*cf.* 76% *vs* 15%). In all instances, conversions were simply determined by comparison of the relative integrals for the ^tBu peaks within the ^1H NMR spectra, with the spectra obtained in deuterated toluene displayed in Figure 33 and Figure 34.



Scheme 185. Examining the catalytic effect exhibited within the oxidation of 3,3-dimethyl-2-butanone (**371**) with *m*CPBA.

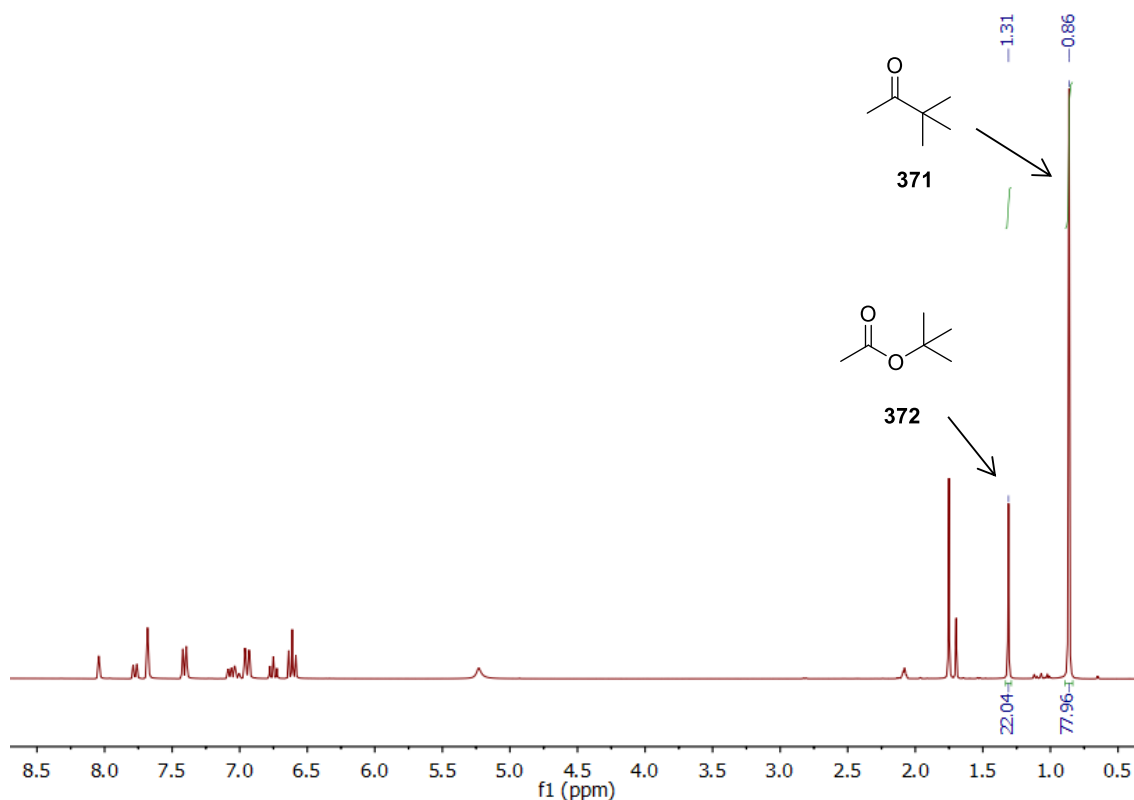


Figure 33. 300 MHz ¹H NMR spectrum obtained in deuterated toluene for the uncatalysed oxidation of 3,3-dimethyl-2-butanone (**371**).

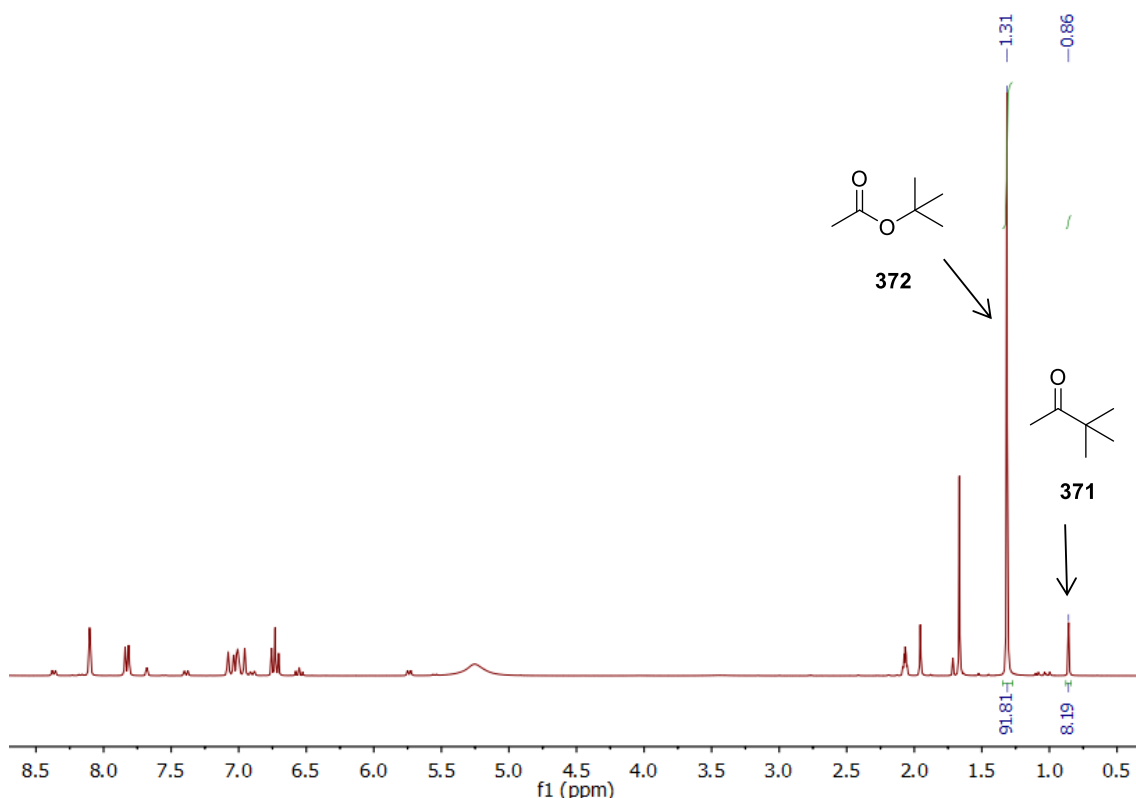


Figure 34. 300 MHz ¹H NMR spectrum obtained in deuterated toluene for the oxidation of 3,3-dimethyl-2-butanone (371) performed in the presence of DMAP.

Armed with the knowledge that the double bond of the enone is not directly involved in the Baeyer-Villiger oxidation, work was focussed on elucidating the origin of the *N*-oxide's catalytic activity. To determine the role of the *N*-oxide it was necessary to ascertain which step of the Baeyer-Villiger oxidation was being catalysed and therefore which transition state the *N*-oxide was interacting with. However, in order to achieve this, knowledge of the rate determining step was required. A general rule for establishing the slow step of the oxidation has not yet been determined, with the rate limiting step remaining unknown for most published systems.^{233,281,292,296} The specific substrate and the reaction conditions under investigation are even known to influence which step is rate determining.^{227,230,232,281,291,296}

Therefore, to examine this feature of the mechanism and determine which step(s) are catalysed, the oxidation of *p*-substituted acetophenones was identified as a suitable mechanistic probe. The entire mechanism for the oxidation of *p*-substituted acetophenone derivatives with peracids in non-polar solvents has been fully characterised both experimentally and computationally, with the rate determining step established for each substrate in the series (Figure 35).^{227,279,291} Specifically, it has been ascertained that the oxidation of acetophenone (374) and its more electron poor derivatives proceeds with rate-determining migration, whilst the rate-determining step switches to addition for the electron rich *p*-methoxy substituted species 373.^{227,279,291} This was

determined from the absence of a KIE for the more electron rich ketone and the deviation from linearity observed within the Hammett plot.^{227,228,242,244,279,291,297,434}

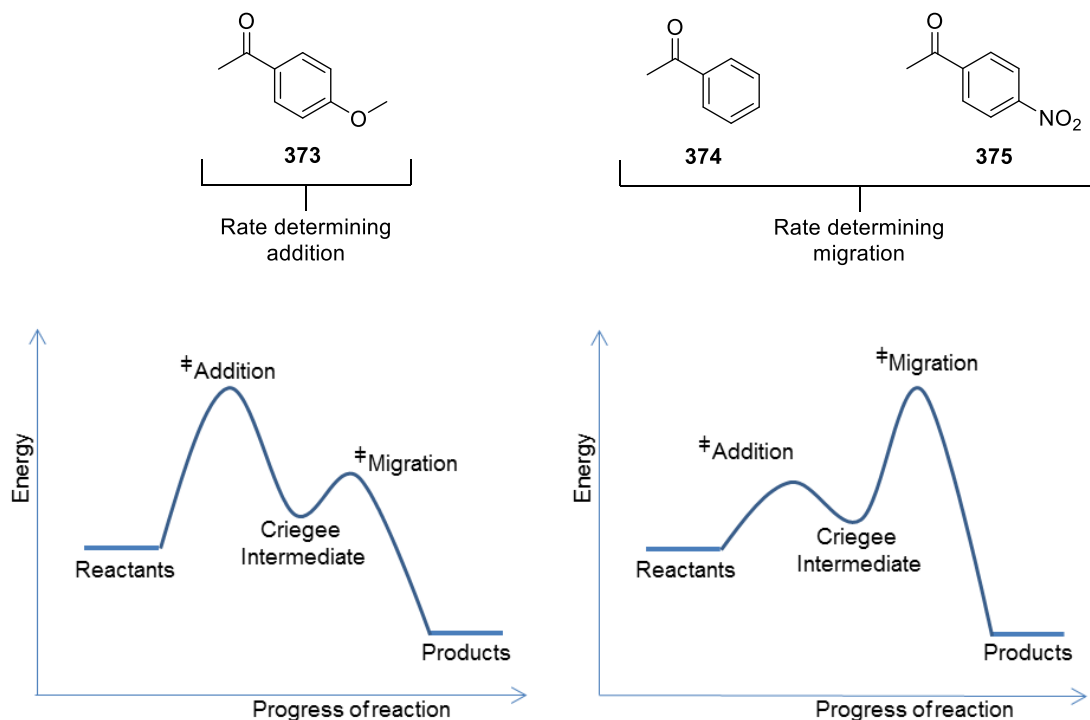
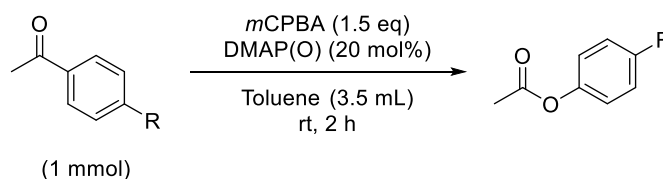


Figure 35. Rate determining steps established for acetophenone derivatives and the corresponding reaction profiles.^{227,279,291}

As the conditions employed within the aforementioned study are comparable to our own system, it may be realistic to suggest that the same reaction kinetics will be applicable. Therefore, it was proposed that by examining the catalytic potential of DMAP/DMAPO within the oxidation of acetophenone (rate determining migration) and *p*-methoxyacetophenone (rate determining addition), it would provide a method for examining which activation energy barrier the *N*-oxide is capable of reducing. Significantly, both DMAP and preformed DMAPO only accelerated the oxidation of *p*-methoxyacetophenone; almost doubling the conversion achieved (Table 13, entry 2). Conversely, both species fail to enhance the reaction rate for the particularly sluggish oxidation of acetophenone, with the reaction even being slightly retarded in the presence of the catalyst (Table 13, entry 1).

Table 13. Examining the catalytic potential of DMAP(O) in the oxidation of acetophenone derivatives.


Entry	Ketone	Conversion, no cat. (%)	Conversion, DMAP (%)	Conversion, DMAPO (%)
1	Acetophenone	7	3	5
2	4-Methoxyacetophenone	50	92	87

Conversions were determined by ¹H NMR spectroscopic analysis.

Therefore, only the oxidation proceeding with rate determining addition was catalysed in the presence of the *N*-oxide. Crucially, this result suggests that the *N*-oxide is only involved with lowering the activation energy barrier for the addition step by interacting with this transition state (Figure 36). Such a result may be anticipated, as proton transfer is often more significant within the initial step.^{232,280,281,291,327} Consequently, it may be inferred that any system catalysed by the *N*-oxide is proceeding *via* rate determining addition. As such, the rate-determining step in the oxidation of (*E*)-4-phenyl-3-buten-2-one (**336**) with *m*CPBA is also proposed to be addition. To further substantiate this hypothesis, the oxidation of 4-nitroacetophenone (**375**), which is known to proceed with rate determining migration, was not catalysed. Conversely, 3,3-dimethyl-2-butanone (**371**) contains an extremely good migrating group ('Bu), which would be expected to accelerate the second step whilst retarding addition of the peracid due to its steric bulk; potentially rendering the addition step rate determining. Accordingly, the oxidation of this saturated substrate was found to be catalysed, as described earlier, indicating that in this instance the activation energy barrier to addition is higher than migration for the uncatalysed reaction. However, it should be cautioned that such mechanistic findings are only applicable to the developed conditions, as a change in any parameter can alter the rate determining step.^{227,228,232,241,244,268,281,292,296,297} Additionally, it is not possible to completely rule out the involvement of the catalyst within the migration step for all substrates or definitively determine that a lack of catalytic effect always signals rate determining migration.

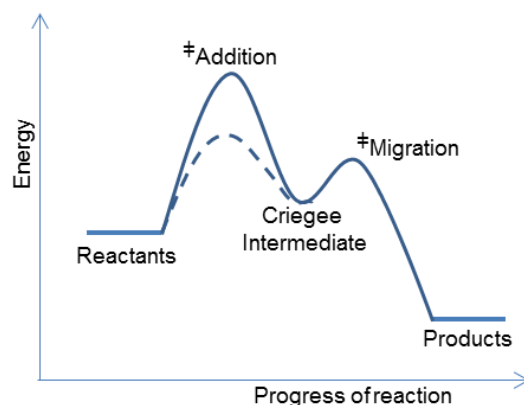
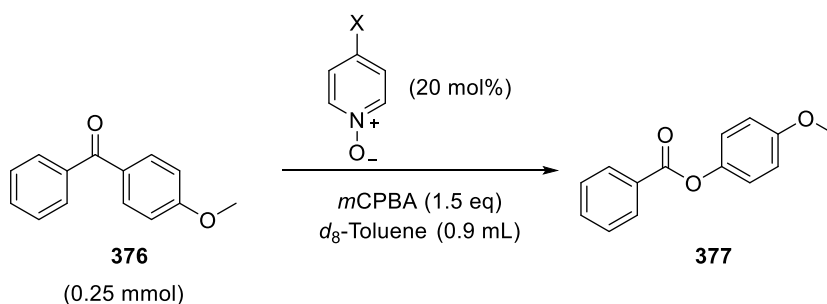


Figure 36. Reaction profile for rate determining addition indicating the role of the *N*-oxide in lowering the activation energy barrier.

In order to further examine the electronic requirements of the catalyst, the oxidation of diaryl ketone **376** was then explored. It was hoped that the reduced electrophilicity of this ketone would allow for a more appreciable disparity in reaction rates to be observed between oxidations promoted by different aromatic *N*-oxide catalysts, whilst also removing the ambiguity introduced by competitive epoxidation reactions. Performing these reactions in deuterated toluene allowed for the conversions to be monitored *in situ*. Interestingly, essentially identical catalytic activity was exhibited by pyridine *N*-oxide derivatives ranging from the highly electron deficient nitro analogue through to the mildly electron rich methyl analogue after both 7 hours (Table 14, entries 1, 4, and 6) and 48 hours (Table 14, entries 2, 5 and 7). The most electron rich derivative, DMAPO, was found to be a far superior catalyst; achieving 36% conversion after 2 hours (Table 14, entry 8). In comparison, to afford a similar level of conversion using any of the other catalysts required an extended reaction time of 48 hours. Thus, the electronic requirements of the catalyst are consistent with the *N*-oxide functioning as a hydrogen bond acceptor, as the oxygen of the more electron rich derivative will possess a higher degree of electron density (see Figure 29).

Table 14. Examining the effect of the amine electronics on the reaction progress for the Baeyer-Villiger oxidation of **376**.



Entry	Catalyst	Time	Ketone 376	Ester 377
1	4-Nitropyridine <i>N</i> -oxide	7h	91	9

2	4-Nitropyridine <i>N</i> -oxide	48h	58	42
3	4-Picoline <i>N</i> -oxide	2h	96	4
4	4-Picoline <i>N</i> -oxide	7h	87	13
5	4-Picoline <i>N</i> -oxide	48h	62	38
6	Pyridine <i>N</i> -oxide	7h	89	11
7	Pyridine <i>N</i> -oxide	48h	59	41
8	DMAPO	2h	64	36

Conversions were determined by ^1H NMR spectroscopic analysis.

The *N*-oxide may be acting to accelerate the addition step by increasing the nucleophilicity of the peracid oxidant, increasing the electrophilicity of the ketone or a combination of both. Several plausible mechanistic proposals consistent with the findings are displayed in Figure 40, Figure 41 and Figure 45, which specifically shows the transition state for the addition step in each case. As previously detailed, in non-polar solvents the uncatalysed peracid oxidation of ketones occurs *via* the 4-membered cyclic transition state shown in Figure 37 (TS1), which is typically prohibitively high in energy.^{280,281,296} In the presence of a carboxylic acid the energy barrier to addition is greatly reduced.^{230,232,280,281,296} The lowest energy transition state identified to date is TS2, for which the carboxylic acid essentially functions as a proton shuttle (Figure 37).^{230,281,292,296} It remains unclear whether the carboxylic acid and *N*-oxide function as co-catalysts within the developed system or whether the carboxylic acid is redundant and just promotes the observed background reaction. Nevertheless, as the oxidation is conducted in a non-polar solvent and in the presence of only a weak acid, it may be concluded that the mechanism in the presence of the *N*-oxide will remain entirely concerted and avoid the formation of dissociated charged ions.

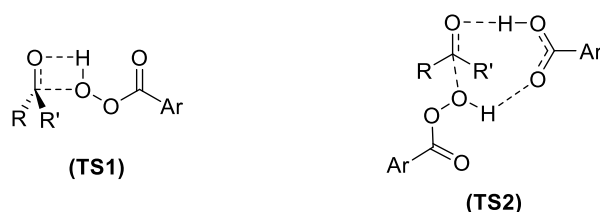


Figure 37. Transition states for the addition of a peracid to a ketone i) in the absence of any additive (TS1) and ii) in the presence of a carboxylic acid (TS2).^{230,233,280,281,291,292}

A number of mechanisms were immediately disregarded based on previous findings and expected reactivity. For instance, the formation of an '*N*-oxide-peroxide' (**378**), which would contain an extremely labile O-O bond and may be subject to analogous acid catalysis, was considered unlikely (Figure 38). Whilst this may represent an oxidant of superior nucleophilicity, the formation of such a highly reactive species has never been observed during the high yielding

synthesis of *N*-oxides under comparable conditions, which may be expected to otherwise degrade the yield. Additionally, due to their low basicity and method of preparation, it is considered implausible that the *N*-oxide is formally deprotonating the peracid to generate a more nucleophilic species.^{6,228,417}

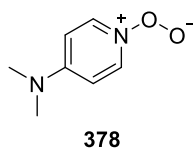


Figure 38. ‘*N*-Oxide peroxide.’

Based on the series of labelling studies outlined previously, it was ascertained that the α,β -unsaturated ketone does not undergo nucleophilic attack by the *N*-oxide in either a 1,2- or 1,4-manner. Therefore, having discounted the formation of covalent interactions between the *N*-oxide and the enone or peracid reagent, it is proposed that the *N*-oxide promotes the Baeyer-Villiger oxidation by aiding the kinetically significant proton transfer event in the addition step *via* hydrogen bonding interactions. Concerted proton transfer is known to occur during heavy atom reorganisation in non-polar solvents and is particularly advanced in the addition step.^{230,280,281,291,326} Whilst the *N*-oxide is thought to facilitate this concerted proton transfer in accordance with the original premise of this work, it is only possible to speculate on the nature of these hydrogen bonding interactions.

1,2-Addition of a nucleophile to a carbonyl group similarly constitutes the first step in the ring opening polymerisation (ROP) of lactides with alcohols.^{435,436} Within the organocatalysed variant, DMAP has been proposed to assume the role of a bifunctional hydrogen bond catalyst (Figure 39).^{435,436} Primarily, this aromatic amine functions as a general base to enhance the nucleophilicity of the initiating or propagating alcohol *via* hydrogen bonding interactions with its sp^2 nitrogen centre.^{435,436} However, by virtue of its acidic *ortho*-hydrogen, DMAP can also function as a weak hydrogen bond donor and is thought to simultaneously enhance the reactivity of the monomer in this manner; enhancing its electrophilicity.^{435,436} Therefore, within the transition state for the addition step of ROP reactions, DMAP is thought to operate as a proton shuttle *via* these two cooperative hydrogen bonding processes.^{435,436} This is similar to the role of carboxylic acids within the Baeyer-Villiger oxidation.

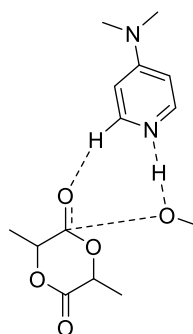


Figure 39. Transition state proposed for the DMAP promoted ROP of a lactide with methanol.^{435,436}

On the basis of this and the greater hydrogen bond basicity of *N*-oxides relative to their parent amine,^{393,394} it was considered feasible that DMAPO may be functioning in an analogous manner within the Baeyer-Villiger oxidation (TS3, Figure 40). Specifically, the *N*-oxide moiety would function as a bifunctional catalyst: abstracting the proton of the peracid to enhance its nucleophilicity, whilst simultaneously increasing the electrophilicity of the ketone *via* hydrogen bonding interactions with its acidic *ortho*-hydrogen.

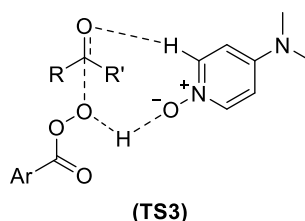


Figure 40. Potential transition state for the addition step of the Baeyer-Villiger oxidation in which the *N*-oxide acts as a bifunctional hydrogen bond catalyst.

Alternatively, it has been postulated that DMAP(O) and *meta*-chlorobenzoic acid may be acting as cooperative hydrogen bond catalysts to promote the Baeyer-Villiger oxidation. This mode of activation has similarly been reported for ring opening polymerisation reactions with a catalytic system comprising of a thiourea and amine.⁴³⁷ Specifically, the *N*-oxide may facilitate abstraction of the peracid hydroxyl proton within the transition state, which serves to enhance the nucleophilicity of the oxidant, whilst the carboxylic acid may simultaneously activate the substrate by functioning as a hydrogen bond donor to the ketone carbonyl. Discrete synergistic general acid-base catalysis (TS4, Figure 41), in which these two hydrogen bonding interactions occur independently and ionic species are formed, would be expected to be disfavoured under the reaction conditions.^{244,280,321,327} In particular, non-polar solvents, such as toluene, are unable to solvate and stabilise such charged species.^{244,280,321,327} Concerted proton transfer between the *N*-oxide and the carboxylic acid within the transition state, which in tandem act as a proton shuttle, is instead more feasible and would regenerate the catalytically active species (TS5, Figure 41).

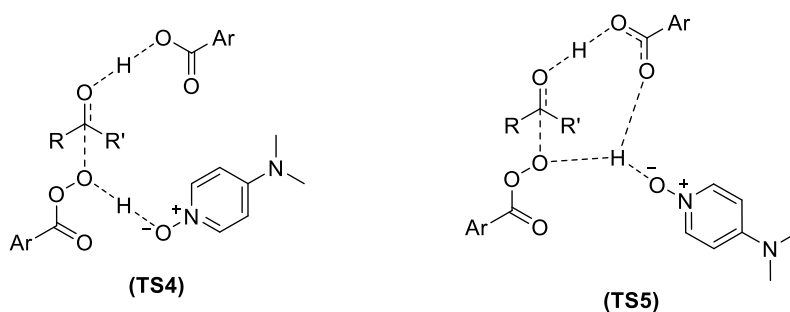


Figure 41. Potential transition states for the addition step of the Baeyer-Villiger oxidation in which the *N*-oxide and carboxylic acid function as co-catalysts.

Salt formation between carboxylic acids and amines may be discouraged to some extent in non-polar solvents such as toluene, as the generation of charged species is unfavourable.⁴³⁸ However, Whiting *et al.* reported that depending on the relative acidity and basicity of these components, an ammonium carboxylate salt may be observed.⁴³⁹ The authors examined the nature of the interactions formed between various amine-carboxylic acid mixtures by ¹H NMR studies and determined that three distinct species may be generated.⁴³⁹ These encompass formation of a: completely ionic salt (**379**), hydrogen bonded complex between the ammonium and carboxylate (**380**) and a hydrogen bonded complex between the amine and carboxylic acid (**381**) (Figure 42).⁴³⁹ Generally, the greater the difference in the pK_{aH} of the base and pK_a of the acid, the more likely salt formation is.^{439,440} Within aqueous solution, a pK_a difference of 3 units is reported to be sufficient to promote salt formation.⁴⁴⁰

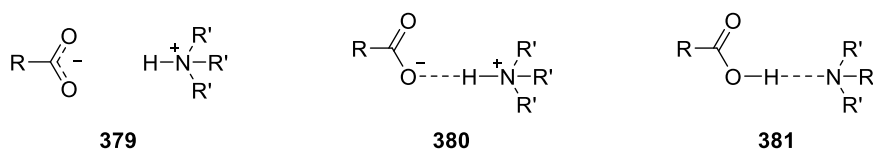


Figure 42. Potential interactions formed between amines and carboxylic acids in solution.⁴³⁹

Therefore, whilst the *N*-oxide is likely to only form hydrogen bonding interactions with the carboxylic acid present in the system (**382**) (DMAPO pK_{aH} = 3.88, *m*CBA pK_a = 3.84),^{392,417} intermolecular proton transfer and thus salt formation may be feasible between DMAP and *m*CBA (pK_{aH} DMAP = 9.58, pK_a *m*CBA = 3.84)^{392,393} (**383**, Figure 43). Very short, intermolecular O-H \cdots O hydrogen bonds have been identified in adducts formed between *N*-oxides and carboxylic acids, which have been characterised both in solution and the solid state.^{398,399} Interestingly, this may reduce the energy barrier to proton transfer.^{391,399} Organic salts of DMAP and various carboxylic acids have also been isolated.⁴⁴¹ These species were found to comprise of a 1:1 complex in which the DMAP is mono-protonated.⁴⁴¹ However, hydrogen bonds were still identified as the major force of attraction between these components.⁴⁴¹

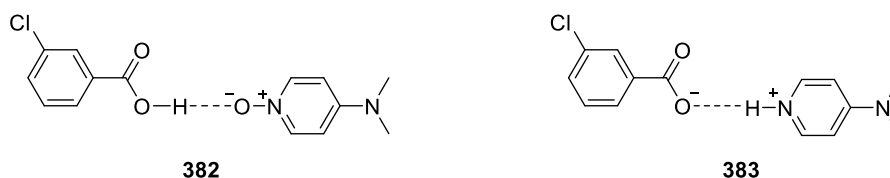


Figure 43. Potential adducts formed between *m*CBA and DMAPO (382) / DMAP (383).⁴⁴¹

Ammonium salts, including ammonium carboxylates, have been employed as catalysts within a variety of reactions involving nucleophilic addition to a carbonyl, such as the ring opening polymerisation of lactides and transamidation to form diketopiperazines.^{435,442-446} Two potential modes of activation have been identified (Figure 44).^{435,443,444} In both proposed mechanisms, the reactivity of the ketone carbonyl is enhanced *via* hydrogen bonding with the labile proton of the ammonium cation.^{435,443,444} It has been postulated that the salt may function as a bifunctional catalyst, with the anion simultaneously acting as a hydrogen bond acceptor to activate the nucleophile.^{435,444} Thus, the properties of both components of the salt would influence the catalytic activity.^{435,442,444} Alternatively, the ammonium salt has been employed as a co-catalyst in conjunction with the corresponding amine, which is proposed to abstract the proton from the nucleophile in the transition state with the anion existing as a spectator only.^{435,443}

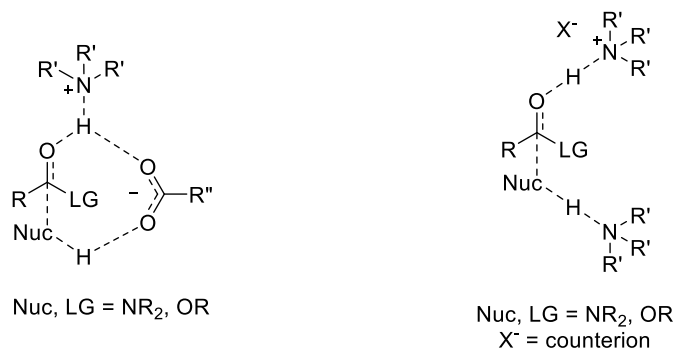


Figure 44. Transition states proposed for ammonium carboxylate promoted nucleophilic additions to carbonyl compounds.^{435,443,444}

Therefore, depending on the relative rate of *N*-oxide and ammonium carboxylate formation under the optimised reaction conditions, it may be plausible that a DMAP-carboxylate salt promotes the Baeyer-Villiger oxidation *via* hydrogen bonding interactions. Due to the large excess of acid present relative to DMAP, negligible free amine would be present to function as a co-catalyst if salt formation was favourable. Therefore, it is proposed that a DMAP-carboxylate salt would function as a bifunctional catalyst to activate both the ketone and peracid nucleophile, as displayed in TS6 (Figure 45).

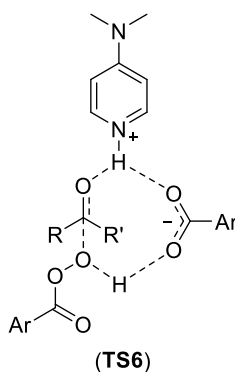


Figure 45. Potential transition state for the addition step of the Baeyer-Villiger oxidation in which a DMAP-*m*CBA salt functions as a bifunctional catalyst.

Thus, the catalytically active species formed from the DMAP pre-catalyst remains unclear. Whilst signals attributable to the pyridine ring protons can be distinguished within ^1H NMR spectra obtained for *in situ* reaction mixtures, the exact identity of the DMAP species has not been determined. Additionally, small quantities of DMAP or a related species [$\delta_{\text{H}} = 8.46$ (2H, d, $J = 7.1$ Hz), 6.68 (2H, d, $J = 6.7$ Hz), 3.18 (6H, s)] was observed alongside the *m*CBA by-product within the precipitated solid when analysed by ^1H NMR spectroscopy in deuterated chloroform. Irrespective of its identity, the catalytic species is thought to function as a hydrogen bond acceptor to facilitate concerted proton transfer within the addition step. Nevertheless, it has been unambiguously established that *N*-oxides promote this transformation and thus the *N*-oxide is referred to as the catalyst herein.

Recent publications have emerged detailing the application of *N*-oxides as hydrogen bond catalysts to promote organic transformations, either *via* stabilisation of an intermediate or assisting proton transfer within the rate determining step.^{67,68,218,219,221,222} Although sparse, this literature precedent helps substantiate the proposed mechanism. For instance, during the course of this work Hammond, Xu and co-workers adopted a similar strategy to accelerate acid promoted reactions involving rate determining proton transfer.^{221,222} Potential additives were targeted based on their ability to act as strong hydrogen bond acceptors (high $\text{p}K_{\text{BHX}}$ values) using Laurence's $\text{p}K_{\text{BHX}}$ database that also fulfilled the criteria of low Brønsted basicity to prevent neutralisation.^{221,222,393,394} Specifically, the authors were interested in identifying additives to improve the efficiency of gold catalysed nucleophilic additions to alkynes/alkenes and transformations involving organo-enamine catalysis.^{221,222} From these studies pyridine *N*-oxide, among other good hydrogen bond acceptors, gave particularly promising results.^{221,222} A comprehensive discussion of the methodology and mechanistic details for these transformations are given in sections 1.4.9 and 1.4.10. Crucially, both of the associated catalytic cycles involve relatively stable protonated, charged intermediates, which are deactivated towards subsequent

reaction.^{221,222} As such species do not readily lose their proton but its removal is required for further transformation to occur, these reactions involve rate determining proton transfer.^{221,222} The authors postulate that the *N*-oxide aids removal of this proton and in doing so reduces the cationic nature of the intermediate by donating electron density into the σ^* antibonding orbital of the intermediate (Figure 46).^{221,222} Notably, within the gold catalysed systems, the hydrogen bond acceptor is thought to act as a proton shuttle during protodeauration.²²¹ Therefore, several parallels can be drawn from these reactions and the carboxylic acid promoted Baeyer-Villiger oxidation of interest. Consequently, it is not unfeasible to suggest that DMAP *N*-oxide is operating in a similar manner within the Baeyer-Villiger oxidation; facilitating the reaction *via* hydrogen bond assisted proton transfer.

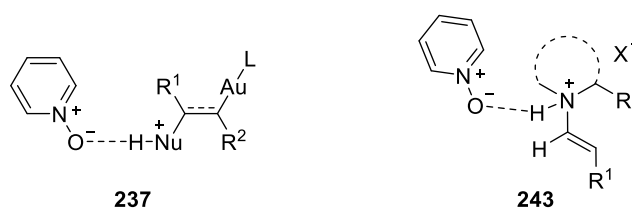


Figure 46. *N*-Oxide additives functioning as hydrogen bond acceptors to improve the efficiency of gold and enamine catalysed reactions.^{221,222}

Previously, in a pioneering study by Stark and co-workers, NMO was found to vastly improve the efficiency of the TPAP-mediated one pot oxidation of primary alcohols to carboxylic acids by functioning as a hydrogen bond catalyst to stabilise the aldehyde hydrate intermediate (Figure 47).^{67,68} It is proposed that these stabilising interactions perturb the equilibrium to some extent towards the normally unstable aldehyde hydrate, which is unfavourable on both entropic and enthalpic grounds; increasing its concentration and in doing so enhancing the reaction rate.^{67,68} *N*-Oxides were again explored for this role based on their low Brønsted basicity and capability to form strong hydrogen bonds, which makes them compatible with the mildly acidic carbonyl hydrate species.^{67,68} Whilst the authors only speculate that the *N*-oxide may function as a catalyst to promote the formation of the aldehyde hydrate (**29**), based on our findings this appears entirely plausible.^{67,68} It may be envisaged that the *N*-oxide facilitates proton transfer from the water nucleophile to the carbonyl oxygen *via* hydrogen bonding interactions. However, this is purely speculative.

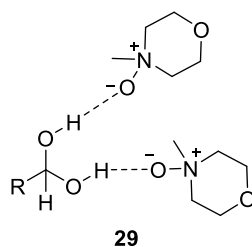


Figure 47. Proposed stabilisation of aldehyde hydrate **29** via hydrogen bonding interactions with NMO.⁶⁸

Furthermore, hydrogen bond catalysis has been proposed as the mode of activation for bifunctional *N,N'*-dioxides in promoting the α -chlorination of cyclic β -ketoesters (**384**), asymmetric domino Michael-alkylation reactions of aryl substituted (*Z*)-bromonitrostyrenes with dimedone and tandem Michael-hemiacetalisation between α -substituted cyano ketones and β,γ -unsaturated α -ketoesters (**385**) (Figure 48, see sections 1.4.7 and 1.4.8).^{2,218-220} Of particular relevance, half an equivalent of carboxylic acid (*p*-BuC₆H₄COOH) is also employed as an additive for the latter reaction; again demonstrating the capability of *N*-oxides to function as hydrogen bond acceptors in the presence of mildly acidic species.²¹⁹

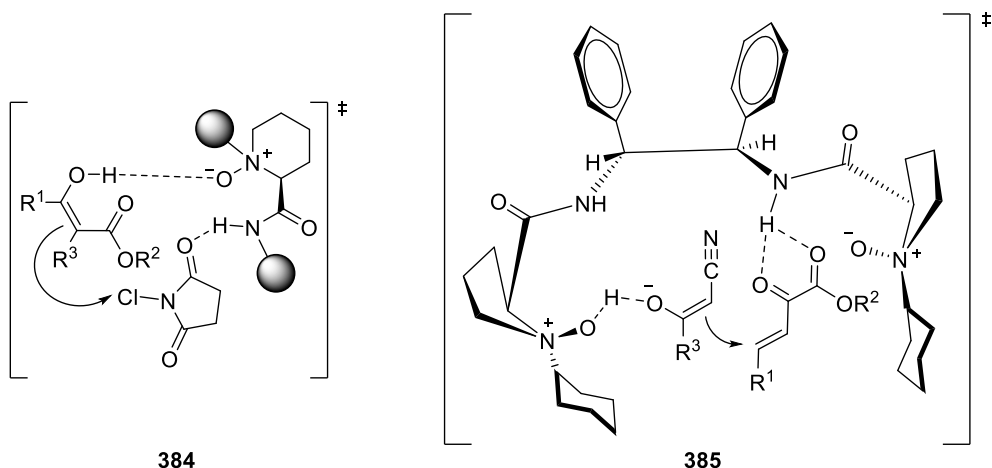
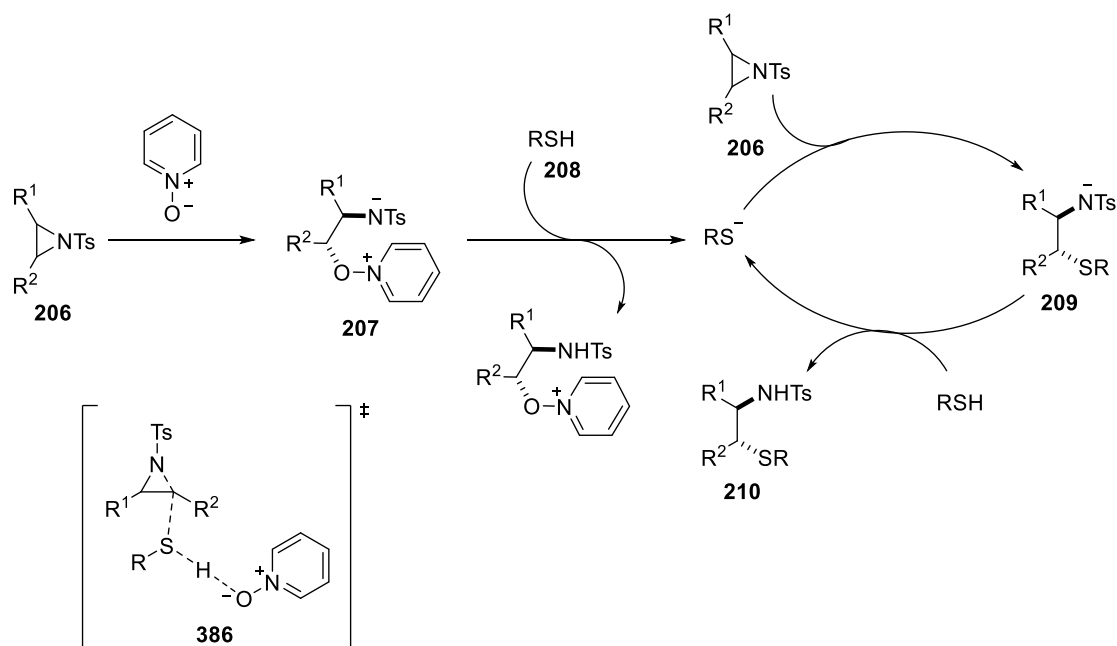


Figure 48. Examples of bifunctional *N,N'*-dioxides proposed to function as hydrogen bond catalysts.^{2,218,219}

Interestingly, the proposed mode of action of the *N*-oxide may also account for the catalysis observed within previously reported reactions, including the ring opening of aziridines by thiols in the presence of pyridine *N*-oxide.²⁰⁸ Whilst the author's proposed mechanism involving initial nucleophilic attack of the aziridine by pyridine *N*-oxide to generate reactive intermediate **207** is entirely feasible,²⁰⁸ it is also plausible that the *N*-oxide is acting as a hydrogen bond catalyst (**386**, Scheme 186). Specifically, the *N*-oxide may function as a hydrogen bond acceptor to facilitate proton transfer from the thiol to the aziridine nitrogen during rate-determining nucleophilic addition (**386**, Scheme 186).

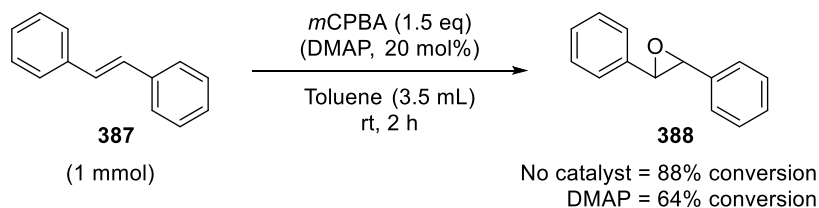


Scheme 186. Potential mechanisms for the *N*-oxide catalysed ring opening of aziridines with thiols.²⁰⁸

Additionally, α -proton transfer has been identified as the rate determining step in the Morita-Baylis-Hillman reaction for the related amine catalysed system.²¹⁰⁻²¹⁴ Therefore, it is hypothesised that, in addition to functioning as a nucleophilic catalyst, the *N*-oxide may aid proton transfer *via* hydrogen bonding; a process that is otherwise achieved by the alcoholic solvent or a further molecule of the aldehyde starting material.²¹⁰⁻²¹⁴

N-Oxides have been found to play a two-fold role in improving the selectivity of the Baeyer-Villiger oxidation of (*E*)-4-phenyl-3-buten-2-one **336** with *m*CPBA for the desired vinyl ester **337**. Firstly, the *N*-oxide enhances the rate of the desired oxidation, transforming **336** into **337**, by interacting with the transition state of the addition step. Additionally, the *N*-oxide appears to inhibit further oxidation, namely epoxidation, of the generated vinyl ester **337**. It was unclear whether the reduced levels of over-oxidation were just an artefact of the enhanced rate of the Baeyer-Villiger oxidation, which would result in greater levels of *m*CPBA consumption and reduce the competitiveness of the epoxidation reaction. Alternatively, it was considered that the DMAP additive may be actively retarding the rate of epoxidation. To elucidate the origin of this effect, the reaction of *trans*-stilbene (**387**) with *m*CPBA was examined both in the presence and absence of DMAP (Scheme 187). This unfunctionalised substrate was chosen based on its known reactivity with *m*CPBA and the lack of potential side reactions.⁴⁴⁷ Interestingly, the oxidation performed in the presence of DMAP afforded inferior conversion into epoxide **388**, with 64% oxidation observed in the presence of the catalyst relative to 88% without. Conversions were determined by comparing the integrals of the peaks at 3.89 ppm and 7.14 ppm, which are

attributable to epoxide **388** and *trans*-stilbene **387** respectively, within the ^1H NMR spectra for the crude reaction mixtures.^{448,449}



Scheme 187. Exploring the effect of DMAP on the epoxidation of *trans*-stilbene.

Therefore, it may be concluded that the use of DMAP retards the epoxidation of alkenes with *m*CPBA. In contrast to the Baeyer-Villiger oxidation, *m*CPBA functions as an electrophilic reagent within such epoxidation reactions. Therefore, it was reasoned that the reduced reactivity observed may be attributed to unfavourable hydrogen bonding interactions between the *m*CPBA and the catalytic species, which would act to enhance its nucleophilic character. Additionally, the concentration of *m*CPBA may have been reduced slightly through reaction with the DMAP to generate the corresponding *N*-oxide.

Based on the mechanistic findings, it is proposed that the *N*-oxide is involved with lowering the activation energy barrier for the addition step *via* the formation of favourable hydrogen bonding interactions. Significantly, it may be inferred that the devised catalytic system will enhance the rate of any Baeyer-Villiger oxidation proceeding with rate-determining addition. Therefore, this presented an opportunity to not only strategically examine the generality of the developed method by targeting substrates expected to exhibit rate-determining addition, but also provided a tool to predict the rate-determining step for each substrate. Such a phenomenon has not been previously reported for the Baeyer-Villiger oxidation. Whilst a plethora of esters and lactones have been synthesized using the Baeyer-Villiger methodology, the rate limiting step has remained elusive for the majority of published examples. Furthermore, it was hoped that the relative migratory aptitude of the vinyl group could be established under the devised conditions. Due to the limited success of α,β -unsaturated ketones within the Baeyer-Villiger oxidation, the relative migratory preference has generally only been reported on a substrate by substrate basis.²⁴²

As well as variations within the reaction conditions, several structural features of the ketone influence the energetics of both transition states, including the sterics, electronics and substitution pattern of the substrate.^{227,228,232,233,291,292,296,329} For the *N*-oxide to promote the oxidation, the activation energy barrier for the addition step within the uncatalysed system must be greater than that for the migration step, as this catalytic species only interacts with the first transition state. Therefore, substrates were generally targeted based on the criteria outlined in Figure 49, which

were expected to help bias the energetics towards rate-determining addition. Interestingly, many of the structural modifications/factors influence the activation energy barrier for both steps.

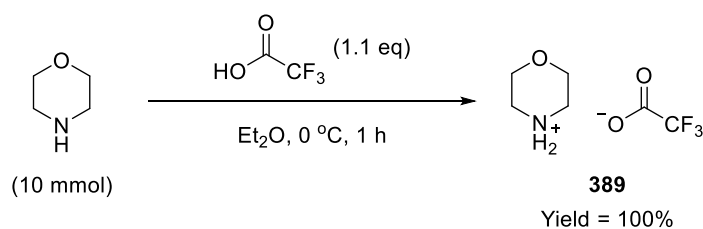
Energy of the migration transition state is reduced when	<ul style="list-style-type: none">• R^M is a good migrating group able to stabilise the forming positive charge (see migratory aptitude sequence)^{228,291}• bulky groups are introduced around the ketone (steric acceleration)²⁹⁴
Energy of the addition transition state is increased when	<ul style="list-style-type: none">• the carbonyl is poorly electropositive due to i) incorporation of strongly electron donating groups, ii) extended conjugation²²⁸• Bulky groups are introduced around the ketone^{228,329}

Figure 49. Structural features of the ketone that influence the energetics of both transition states of the Baeyer-Villiger oxidation.

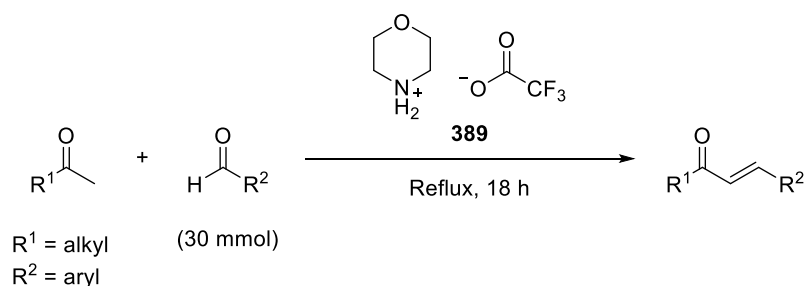
Quite crudely, rate determining addition should become increasingly likely with an increase in: the steric bulk around the carbonyl carbon, conjugation or the electron donating capacity of the substituents, which acts to reduce the electrophilicity of the ketone and/or facilitate migration. Such strategies were implemented whilst examining the substrate scope.

2.3.5 Synthesis of starting materials

Where α,β -unsaturated ketones were not commercially available, they were synthesized *via* the aldol condensation of an aromatic aldehyde with the appropriate ketone; catalysed by either morpholinium trifluoroacetate (Table 15, Method A) or sodium hydroxide (Table 15, Method B). According to a literature procedure published by List *et al.*, morpholinium trifluoroacetate (**389**) was prepared in quantitative yield by slow addition of an ether solution of trifluoroacetic acid to an ether solution of morpholine at 0 °C (Scheme 188).⁴⁵⁰ After stirring for 1 hour, the precipitate was filtered under nitrogen and washed with ether to afford the desired salt cleanly as a white solid.⁴⁵⁰ Aldol condensations promoted by morpholinium trifluoroacetate (**389**) were performed in acetone at reflux for 18 hours (Scheme 189).⁴⁵⁰ The analytically pure α,β -unsaturated ketones were then obtained *via* a liquid-liquid extraction and subsequent purification by flash column chromatography.

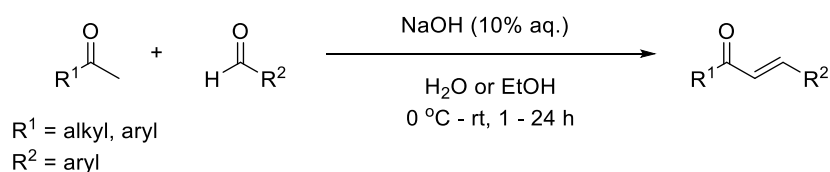


Scheme 188. Preparation of morpholinium trifluoroacetate (389).⁴⁵⁰



Scheme 189. Aldol condensations promoted by morpholinium trifluoroacetate (389) (Method A).⁴⁵⁰

Alternatively, for the base promoted aldol condensations, a 10% aqueous sodium hydroxide solution was added dropwise to a mixture of the appropriate aldehyde and ketone in water or ethanol at 0 °C (Scheme 190). The reaction mixture was then stirred at room temperature before being purified and isolated by either filtration, column chromatography or distillation depending on the nature of the product.

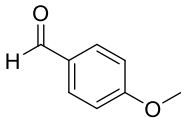

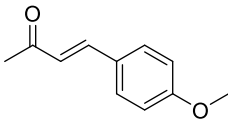
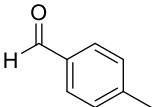

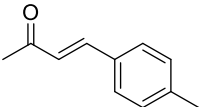
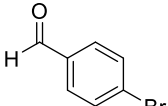

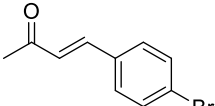
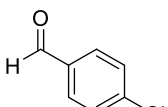

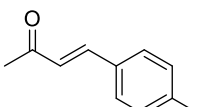
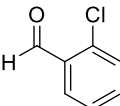

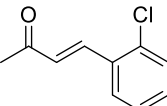
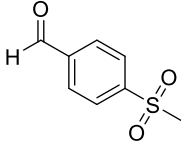

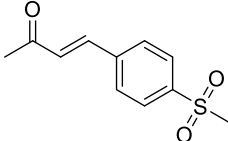


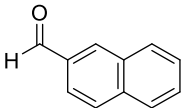

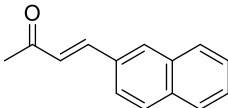
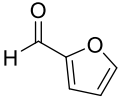

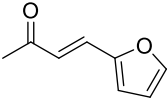
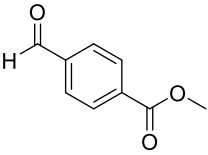

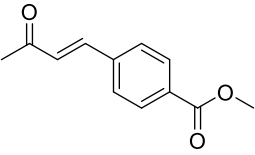
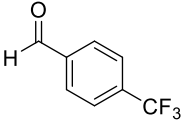

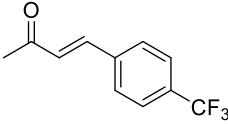
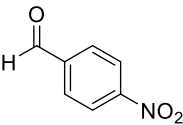

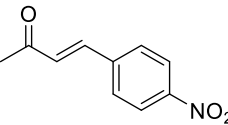
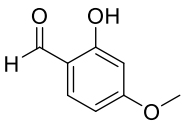

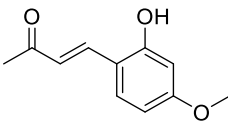
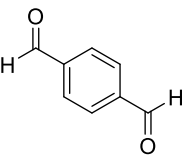

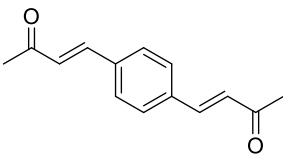
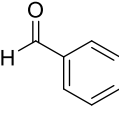

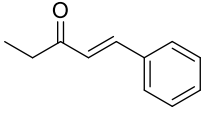
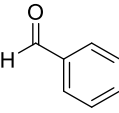

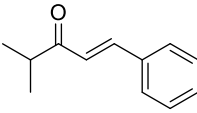
Scheme 190. Base promoted aldol condensations (Method B).

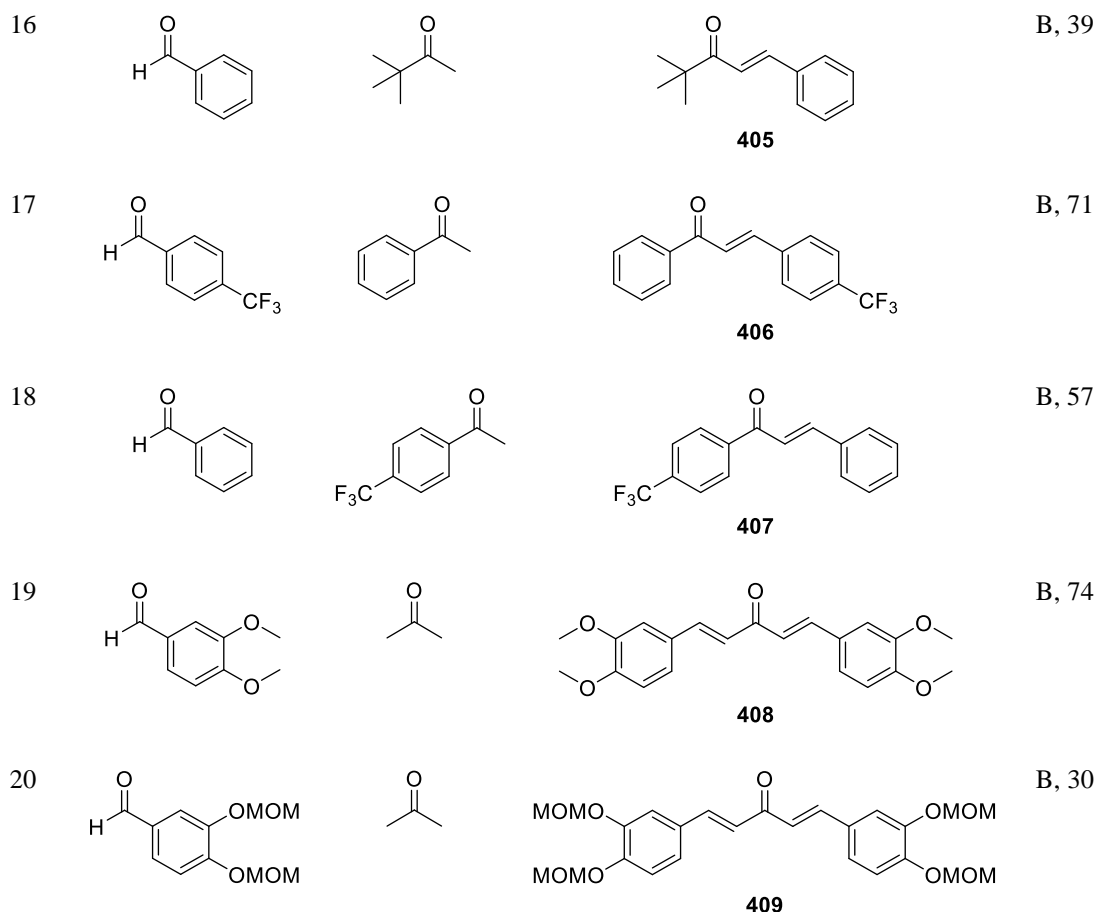
α,β -Unsaturated ketones **390-409** were afforded exclusively as the (*E*)-diastereomer, with the *trans* configuration confirmed by the characteristically large vicinal coupling constants between the vinyl protons (> 16 Hz). The identity of the isolated compounds were confirmed by comparison of their spectroscopic data with that reported in the literature. Disubstituted α,β -unsaturated methyl ketones (**390-401**), prepared from the reaction of acetone with the appropriate aromatic aldehyde, were typically afforded in moderate to excellent yields of up to 95% (Table 15, entries 1-12). Although symmetrical diketone **402** was isolated in good yield from the corresponding dialdehyde, small amounts (13%) of the mono-aldol product (**410**) were also obtained (Table 15, entry 13). In some instances unsymmetrical aliphatic ketones did not provide

a regioselective reaction, which contributed to the slightly reduced isolated yields achieved for the desired products (**403-405**, Table 15, entries 14-16). Chalcone derivatives **406** and **407**, as well as functionalised dibenzylideneacetone derivatives **408** and **409** were accessed with varying degrees of success (Table 15, entries 17-20).

Table 15. α,β -Unsaturated ketones prepared *via* aldol condensation reactions.

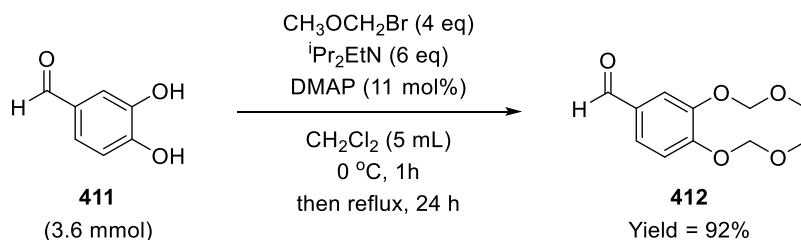
$\text{R}-\text{C}(=\text{O})-\text{CH}_3 + \text{H}-\text{C}(=\text{O})-\text{Aryl} \xrightarrow[\text{Method B}]{\text{Method A or Method B}} \text{R}-\text{C}(=\text{O})-\text{CH}=\text{CH}-\text{Aryl}$				
Entry	Aldehyde	Ketone	α,β -Unsaturated ketone	Method, Yield (%)
1			 390	B, 87
2			 391	B, 67
3			 392	B, 54
4			 393	B, 93
5			 394	B, 72
6			 395	B, 8

7			 396	A, 89
8			 397	A, 77
9			 398	A, 43
10			 399	A, 95
11			 400	A, 66
12			 401	A, 21
13			 402	A, 63 ^a
14			 403	A, 56
15			 404	A, 38



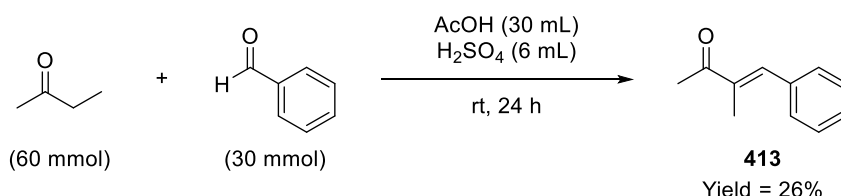
^a13% of the mono-aldol product (**410**) was also isolated.

The methoxymethyl (MOM) acetal protected aldehyde (**412**) employed in the synthesis of dibenzylideneacetone derivative **409** was initially prepared from commercially available 3,4-dihydroxybenzaldehyde (**411**) (Scheme 191). Accordingly, 3,4-dihydroxybenzaldehyde was treated with diisopropylethylamine and catalytic quantities of DMAP in dichloromethane followed by the dropwise addition of bromomethyl methyl ether at 0 °C.⁴⁵¹ Refluxing the mixture for 24 hours provided **412** in 92% yield upon purification by flash column chromatography.



Scheme 191. Synthesis of methoxymethyl acetal (MOM) protected aldehyde (**412**).⁴⁵¹

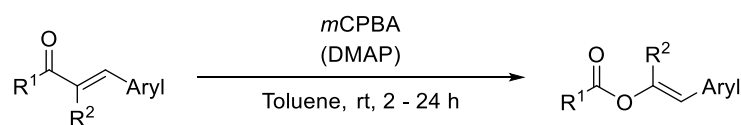
Trisubstituted α,β -unsaturated methyl ketone **413** was prepared *via* an acid catalysed aldol condensation (Scheme 192).⁴⁵² Sulfuric acid was added dropwise to a stirred solution of benzaldehyde and 2-butanone in glacial acetic acid and the mixture was stirred at room temperature for 24 hours.⁴⁵² After quenching the reaction mixture with aqueous sodium hydroxide and extracting into diethyl ether, the crude residue was purified by flash column chromatography to afford **413** as a colourless oil in 26% isolated yield.



Scheme 192. Synthesis of **413** *via* an acid catalysed aldol condensation.⁴⁵²

2.3.6 Substrate scope

Oxidations were performed by adding the appropriate ketone to a vigorously stirred suspension of *m*CPBA and where applicable DMAP in toluene (Scheme 193). Whilst the mixture was homogenous initially, a white precipitate was observed in all instances as the reaction progressed, generating a slurry. After stirring the reaction mixture at room temperature for the specified period of time, sufficient quantities of saturated aqueous bicarbonate solution were added to ensure that all of the precipitate had dissolved. The crude reaction mixture was then extracted into ethyl acetate and the ratio of products were determined by ¹H NMR spectroscopic analysis in deuterated chloroform. The identity of the species formed were established using the chemical shifts of the unfunctionalised derivatives generated from the oxidation of (*E*)-4-phenyl-3-buten-2-one (**336**) as a guideline. Where the vinyl esters were isolated, purification was achieved by flash column chromatography and the compounds were fully characterised, with all data in accordance with that provided within available literature reports. The characteristic spectroscopic markers used to confirm the presence of the vinyl ester moiety included: i) the upfield shift of the peak attributed to the β -vinylic proton in conjunction with the slightly reduced coupling constant between the vinyl protons within the ¹H NMR spectra, ii) the upfield shift of the carbonyl carbon resonance within the ¹³C NMR spectra and iii) the higher carbonyl stretching frequency within the IR spectra.



Scheme 193. Conditions employed for examining the substrate generality of the devised Baeyer-Villiger oxidation protocol.

2.3.6.1 Baeyer-Villiger oxidation of α,β -unsaturated methyl ketones

Initially, the electronic requirements of the oxidation were examined by applying the developed methodology to a range of *para*-substituted derivatives of (*E*)-4-phenyl-3-buten-2-one (**336**), which were furnished with both electron donating and withdrawing groups of varying strength (Table 16). It was of particular interest to determine at which point in the sequence the mechanism changed from rate-determining addition to rate determining migration. Figure 50 outlines the labelling system used in subsequent tables to refer to each of the potential oxidation products.

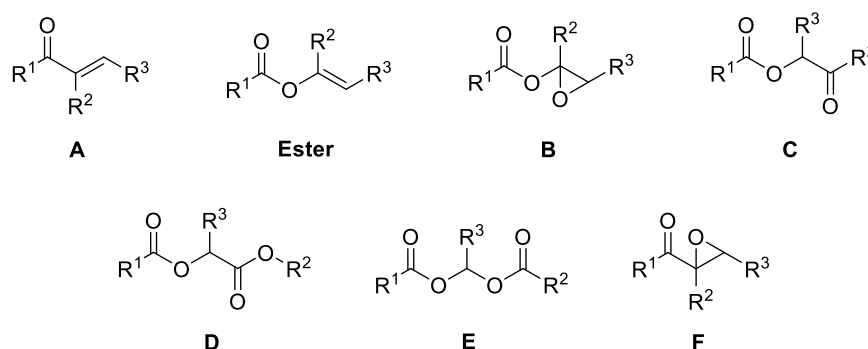
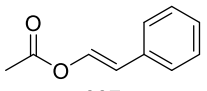
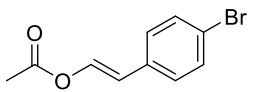
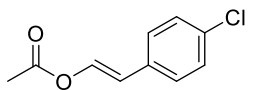
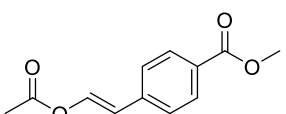
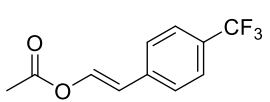
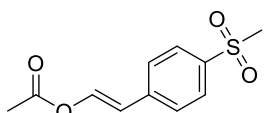
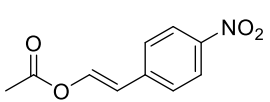


Figure 50. Labelling system used for potential products within substrate scope studies.

Table 16. Examining stereoelectronic effects on the Baeyer-Villiger oxidation of α,β -unsaturated methyl ketones.

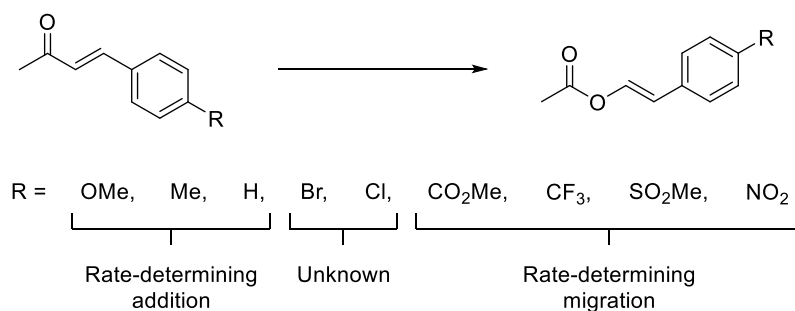
Entry	Vinyl Ester	Conditions	A	Ester	B	C	D	E	F
1	 414	No cat, 2h	53	14	-	5	1	27	n.d.
		DMAP, 2h	12	82	-	1	-	5	n.d.
2	 415	No cat, 2h	38	22	1	9	2	21	7
		DMAP, 2h	8	85	-	2	-	2	3

3	 337	No cat, 2h	28	30	16	13	6	4	3
		DMAP, 2h	6	79	14	-	-	-	1
4	 416	No cat, 2h	15	48	31	1	2	-	3
		DMAP, 2h	10	75	14	-	-	-	1
5	 417	No cat, 2h	16	39	25	9	4	4	3
		DMAP, 2h	10	77	12	-	-	-	1
6	 418	No cat, 24h	13	34	48	1	-	-	4
		DMAP, 24h	19	71	8	-	-	-	2
7	 419	No cat, 24h	13	45	41	-	-	-	1
		DMAP, 24h	30	63	6	-	-	-	1
8	 420	No cat, 24h	17	55	26	-	-	-	2
		DMAP, 24h	64	35	1	-	-	-	-
9	 421	No cat, 24h	10	51	37	-	-	-	2
		DMAP, 24h	58	38	3	-	-	-	1

Product ratios were determined by ^1H NMR spectroscopic analysis.

As can be seen from the results in Table 16, the DMAP additive only catalysed the oxidation of the parent substrate and its more electron rich analogues, specifically the *p*-methyl and *p*-methoxy species (Table 16, entries 1-3). Therefore, it may be anticipated that the oxidation of such species proceeds with rate determining addition (Scheme 194). Conversely, the level of starting material consumption was found to be greater in the absence of the catalyst for substrates bearing a relatively strong electron withdrawing functionality (Table 16, entries 6-9). Variation in the electronics of the migrating group is known to impart a far greater effect on the energy barrier of the second step, with electron withdrawing groups destabilising the developing positive charge and therefore increasing the activation energy barrier for the second step.^{227,232,291,326} Due to the absence of a catalytic effect within the oxidation of methyl 4-[(1*E*)-3-oxobut-1-en-1-yl]benzoate **398** and its more electron poor congeners (Table 16, entries 6-9), it may be surmised that under

the developed conditions the transition state for the migration becomes higher in energy once reaching this electronic scenario and the rate determining step changes from addition to migration. However, in cases where the *para*-substituent is a mildly electron withdrawing halogen the influence of the DMAP is ambiguous (Table 16, entries 4 and 5). Whilst slightly higher conversion of the starting material was observed in the presence of DMAP, it is unclear whether this is due to an increase in the rate of the desired Baeyer-Villiger oxidation or a factor of the reduced over-oxidation, which otherwise competitively consumes the *m*CPBA reagent.



Scheme 194. Predicted rate determining step for the Baeyer-Villiger oxidation of α,β -unsaturated methyl ketones based on the catalytic effects observed.

Interestingly, for the reactions performed in the absence of catalyst, electron neutral substrates ($\text{R} = \text{H}$) or those bearing mildly deactivating groups ($\text{R} = \text{Br}, \text{Cl}$) underwent the most facile Baeyer-Villiger oxidation (Table 16, entries 3-5). Introducing either more strongly electron withdrawing groups or electron donating groups was found to retard the reaction rate, which represents an unusual trend and is an artefact of the change in mechanism (Figure 51). For the electron poor analogues, which are thought to proceed *via* rate determining migration, the introduction of more strongly electron withdrawing functionality further retards migration and thus the overall rate, as this functionality destabilises the migrating group. The associated reduction in conversion can be overcome in part by leaving the reactions for an extended time of 24 hours (Table 16). Alternatively, for electron rich substrates, which may proceed *via* a mechanism involving rate determining addition, an increase in the electron donating ability of the substituent presumably reduces the electrophilicity of the ketone and retards addition and thus the overall reaction rate. In this instance, the reaction rate and associated conversion could be improved by addition of the DMAP catalyst.

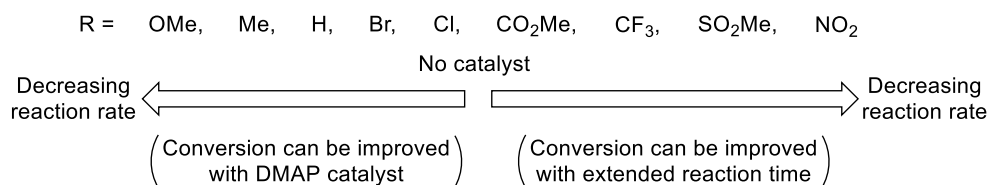


Figure 51. Influence of electronics on the rate of oxidation of α,β -unsaturated methyl ketones and the influence of DMAP on the reaction selectivity.

In the absence of catalyst, considerable undesired over-oxidation of the vinyl ester was observed (Figure 52). With regard to electron poor substrates, high levels of the epoxy ester by-product were generated. Alternatively, for substrates possessing relatively high levels of electron density within the conjugated system, a multitude of different over-oxidation products were observed (Table 16, entries 1-5). In particular, the most electron-donating substituents promoted the entire sequence of transformations; affording high levels of formate ester (Table 16, entries 1 and 2), whilst the aldehyde was the more predominant over-oxidation product for the parent and *para*-halogenated substrates (Table 16, entries 3-5). Collectively, these findings suggest that electron withdrawing groups inhibit rearrangement of the epoxy ester, whilst electron donating groups promote the second Baeyer-Villiger event to produce the formate ester.

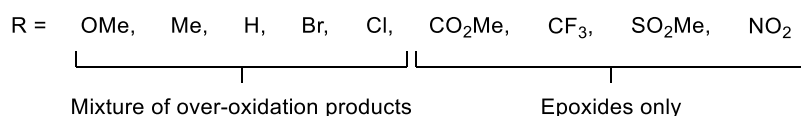


Figure 52. Effect of electronics of the α,β -unsaturated methyl ketones on the identity of the by-products formed.

Although in some instances the rate of reaction was not increased in the presence of DMAP, this additive was found to universally inhibit undesired oxidation of the desired vinyl ester. In the case of substrates **398** and **399**, DMAP provided improved selectivity for the corresponding vinyl esters **418** and **419** (Figure 53, Table 16, entries 6 and 7).

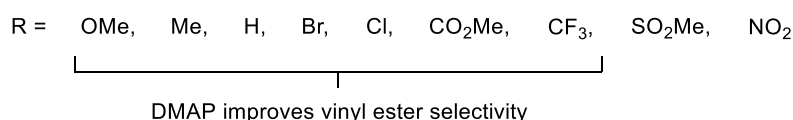
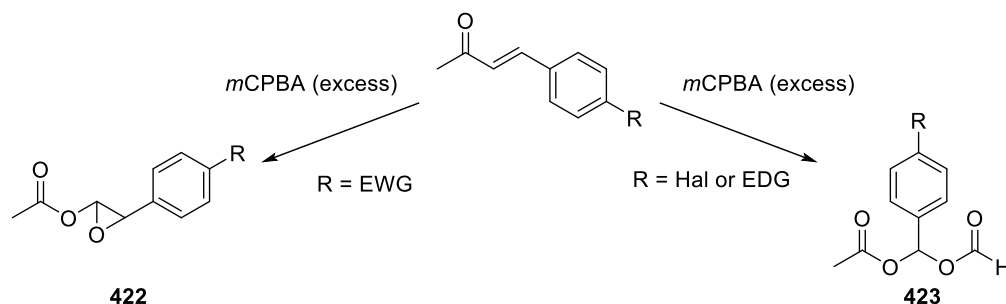


Figure 53. α,β -Unsaturated methyl ketones identified that exhibit improved selectivity for the vinyl ester in the presence of DMAP.

It may be anticipated that repeating the uncatalysed variant with a large excess of *m*CPBA reagent may allow for electron poor substrates to be selectively converted into the corresponding epoxy esters (**422**) (Scheme 195, Table 16, entries 6-9). Alternatively, under similar conditions the oxidation of electron rich substrates and those bearing mildly deactivating groups should allow

for functionalised formate esters of the form **423** to be accessed in high selectivity (Table 16, entries 1-5).



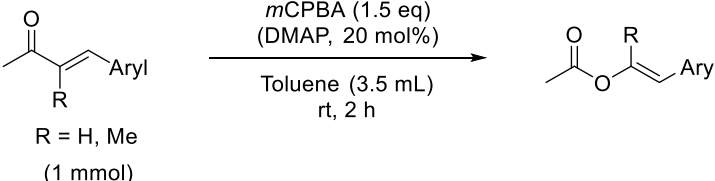
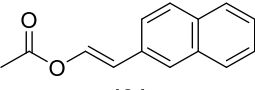
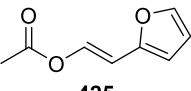
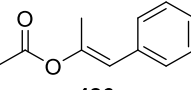
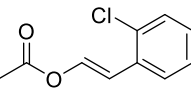
Scheme 195. Potential method for accessing functionalised epoxy esters (**422**) and formate esters (**423**).

Due to the poor solubility of the sulfone substituted α,β -unsaturated methyl ketone **395** in toluene, the oxidation was also investigated in dichloromethane. This solvent was previously identified as a viable alternative, achieving good conversion for the parent substrate (Table 8). However, the reaction rate and selectivity could not be improved for the vinyl ester (**420**) using this alternative approach, even for extended reaction times or using a greater excess of *m*CPBA (2 equiv.).

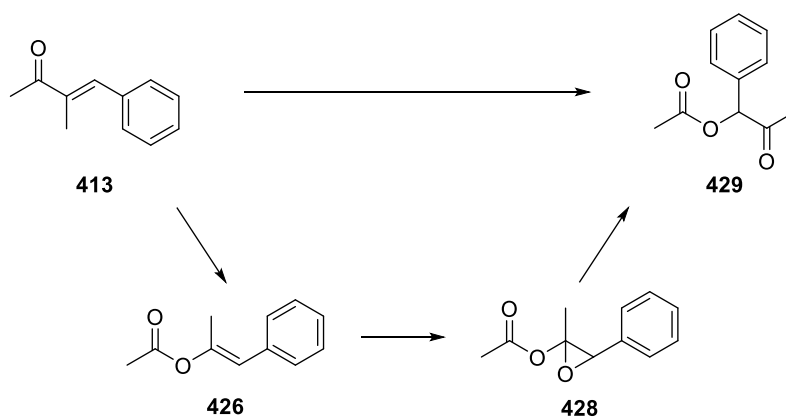
Armed with the knowledge that the Baeyer-Villiger oxidation of electron neutral and electron rich α,β -unsaturated methyl ketones are promoted by the *N*-oxide, other unfunctionalised aromatic systems as well as the substitution pattern of the double bond were investigated (Table 17, entries 1-3). In the presence of DMAP the oxidation of naphthalene derivative **396** proceeded with a much enhanced rate relative to the background and gave exceptional selectivity for the desired vinyl ester **424** (89%) (Table 17, entry 1). Pleasingly, this methodology was also successfully extended to furyl species **397**, with this heteroaromatic ring known to be susceptible to both acid catalysed degradation and oxidation in the presence of *m*CPBA.⁴⁵³ In this instance the catalytic effect is particularly evident, with only 4% conversion of the starting material into the corresponding aldehyde by-product observed in the absence of DMAP (Table 17, entry 2). Conversely in the presence of this additive, 69% of the starting material was converted exclusively into the desired vinyl ester **425**. The developed methodology was also found to be amenable to trisubstituted α,β -unsaturated methyl ketones, with complete consumption of the starting material and minimal over-oxidation observed in the presence of DMAP for **413** (Table 17, entry 3). Relative to the disubstituted analogue, reasonably large quantities of a more stable epoxy ester (**428**) were observed in the uncatalysed reaction. This may be accounted for on the basis of the enhanced nucleophilicity of the more electron rich, trisubstituted double bond. It is also interesting to note that epoxide **428** could rearrange to give β -ketoester **429**, presumably *via* the same mechanism outlined for the structurally related aldehyde **341** (Scheme 196).

Although the rate determining step could not be predicted, the oxidation of *o*-chloro species **394** was identified as an important transformation to allow for the effects of the aryl substitution pattern on reactivity and product distribution to be examined. In the presence of the catalyst, this *ortho*-substituted species was slightly more sluggish to react than the corresponding *para*-substituted regioisomer (Table 17, entry 4 vs Table 16, entry 5), with 25% starting material remaining for the former after 2 hours and only 10% for the latter. Additionally, for the uncatalysed reaction, over-oxidation and therefore the formation of multiple by-products was dramatically reduced for the *ortho*-substituted substrate; presumably due to steric hindrance of the vinyl moiety imparted by the relatively large *o*-chloro substituent. Nevertheless, superior selectivity for the vinyl ester product (**417** / **427**) was achieved for both the *para*- and *ortho*-substituted regioisomers in the presence of DMAP.

Table 17. Further examining the substrate generality of the developed oxidation protocol for α,β -unsaturated methyl ketones.

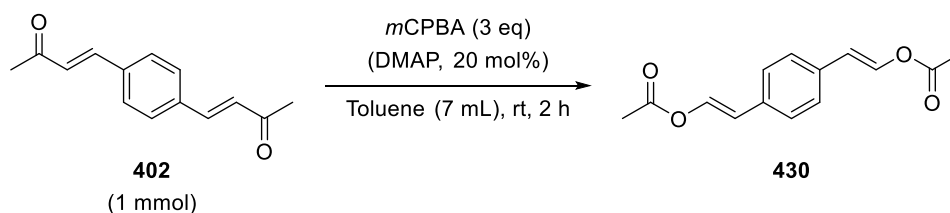
 <p>R = H, Me (1 mmol)</p>									
Entry	Vinyl Ester	Catalyst	A	Ester	B	C	D	E	F
1		-	36	29	1	9	2	19	4
		DMAP	2	89	3	4	-	-	2
2		-	96 ^a	-	-	4	-	-	-
		DMAP	31 ^a	69	-	-	-	-	-
3		-	14	27	43	6 ^b	-	-	10
		DMAP	-	87	11	-	-	-	2
4		-	38	48	12	-	-	-	2
		DMAP	25	66	7	-	-	-	2

Product ratios were determined by ¹H NMR spectroscopic analysis. ^aSmall amounts of unidentifiable by-products observed. ^bConversion into ketone **429**.



Scheme 196. Proposed Baeyer-Villiger oxidation, epoxidation and rearrangement of trisubstituted α,β -unsaturated ketone 413 to afford β -ketoester 429.

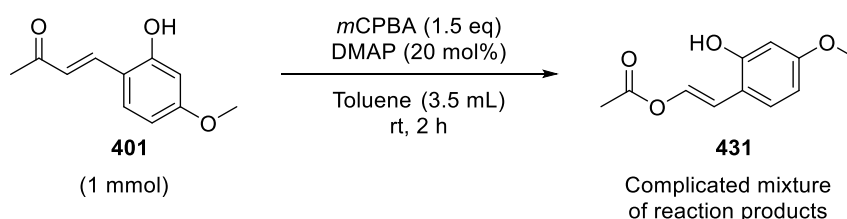
The Baeyer-Villiger oxidation of symmetrical diketone **402** was also successfully catalysed by DMAP (Scheme 197). In this instance 3.0 equivalents of *m*CPBA was employed and the amount of solvent was doubled to account for this. Analysis of the ^1H NMR spectrum for the control reaction indicated that a complex mixture of reaction products had formed, resulting in a number of overlapping vinyl signals at chemical shifts characteristic of both an ester and ketone. Additionally, considerable quantities of an aldehyde based species could also be identified from the characteristic downfield proton shift. In contrast, the crude reaction mixture for the catalysed system contained primarily the diester product **430** in addition to small quantities of other related species; the exact identity of which could not be established. Due to the complexity of the spectra in both cases, exact conversions could not be ascertained. This complexity arises from the number of potential transformations available to each unsaturated ketone moiety and the number of potential combinations of the resultant functionalities; affording various symmetrical and unsymmetrical products.



Scheme 197. Extension of the developed Baeyer-Villiger methodology to symmetrical diketone 402.

Vinyl ester **431** was identified as an interesting synthetic target, as it is a natural product isolated by the group of Jain and Srivastava from the heartwood of *Aegle marmelos* Corr (Scheme 198).⁴⁵⁴ Whilst the presence of DMAP provided a much cleaner reaction profile, disappointingly multiple unidentifiable reaction products were still formed, as determined by ^1H NMR spectroscopic analysis of the crude reaction mixture. It is thought that the presence of the hydroxyl group may

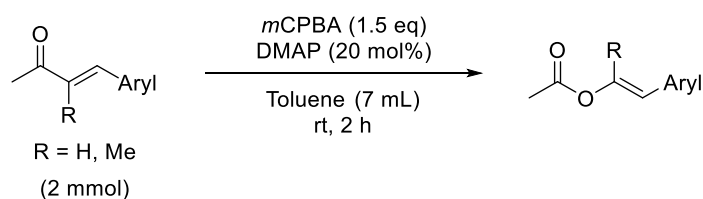
have been responsible for the observed degradation and therefore this functionality may not be amenable to the oxidation conditions. Accordingly, it has been reported that phenols are readily oxidised with peracids.²⁹⁵



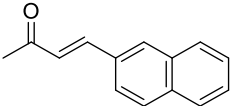
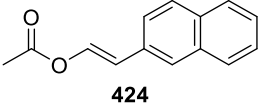
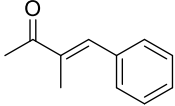
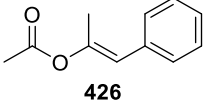
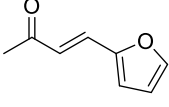
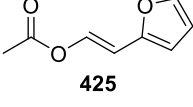
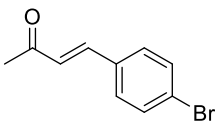
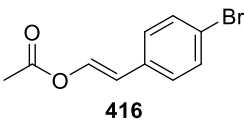
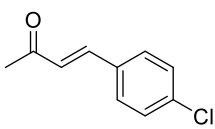
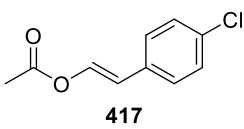
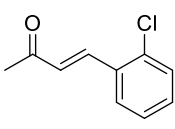
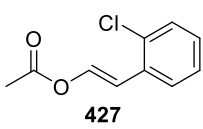
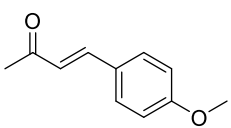
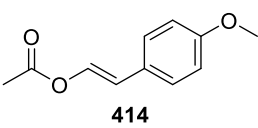
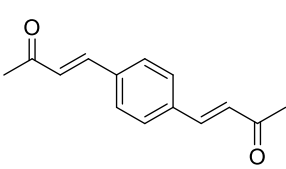
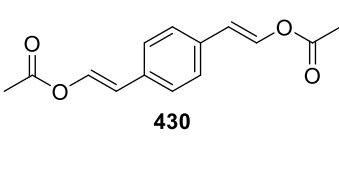
Scheme 198. Attempted synthesis of vinyl ester **431** using the developed oxidation protocol.

Having ascertained that DMAP may greatly enhance the selectivity of the Baeyer-Villiger oxidation of α,β -unsaturated methyl ketones for the corresponding vinyl acetates, either by catalysing the reaction, preventing over-oxidation or a combination of both, attempts were made to isolate these unsaturated esters (Table 18). For substrates containing an electron rich or mildly electron poor aromatic substituent, the reactions were performed at room temperature in the presence of DMAP for 2 hours. Pleasingly, these vinyl acetates were typically isolated in moderate to good yields (52-71%). However, diester **430** was isolated in a disappointing 30% yield, primarily arising from problems encountered during purification rather than poor conversion (Table 18, entry 10). In this instance, co-elution of the symmetrical desired product with a related species, which was thought to be an unsymmetrical ester containing product, degraded the yield.

Table 18. Baeyer-Villiger oxidation of a range of α,β -unsaturated methyl ketones with *m*CPBA in the presence of DMAP.



Entry	α,β -Unsaturated ketone	Vinyl Ester	Yield (%)
1	<p style="text-align: center;">336</p>	<p style="text-align: center;">337</p>	69
2	<p style="text-align: center;">391</p>	<p style="text-align: center;">415</p>	70

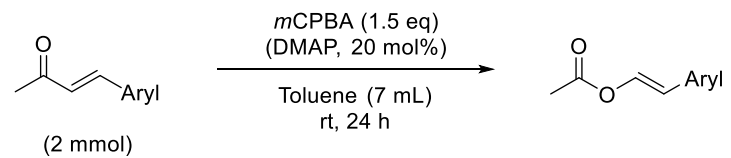
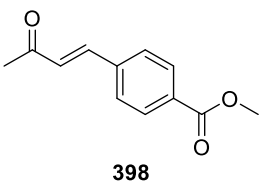
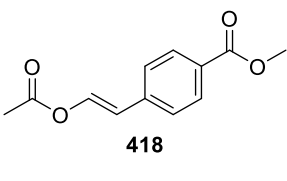
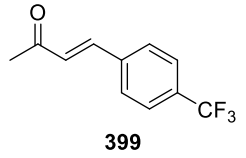
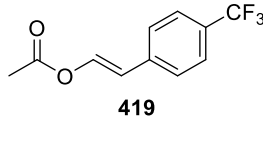
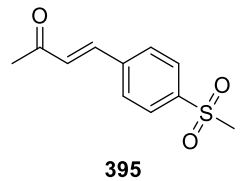
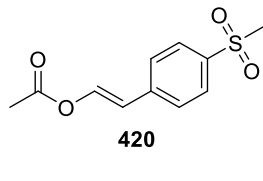
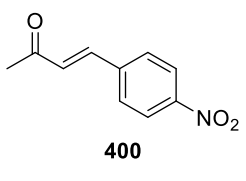
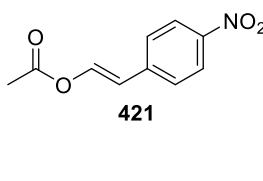
3	 396	 424	71
4	 413	 426	66
5	 397	 425	52
6	 392	 416	69
7	 393	 417	71
8	 394	 427	54
9	 390	 414	62
10	 402	 430	30 ^a

^aPerformed using double the amount of *m*CPBA (3.0 equiv.) and toluene (7 mL).

418 and **419** were isolated in moderate yield (55 and 53%) when the corresponding ketones were applied to the DMAP protocol for an extended time of 24 hours (Table 19, entries 1 and 2). Although the oxidation of electron poor *p*-sulfone (**395**) and *p*-nitro (**400**) derivatives required the absence of catalyst and extended reaction times (24 h) to achieve superior results, the isolation of **420** and **421** was still of interest due to problems otherwise accessing such deactivated vinyl esters

via Baeyer-Villiger oxidation. Moderate yields for these substrates were subsequently achieved (Table 19, entries 3 and 4), with (*E*)-2-(4-methanesulfonylphenyl)ethenyl acetate (**420**) representing a novel compound. In some instance, negligible quantities of the (*Z*)-stereoisomer were observed for the *p*-nitro derivative (**421**). As the exact ratio varied between different batches of starting material it is thought that the absolute stereochemistry may follow through from the starting material, rather than being the result of isomerisation during the Baeyer-Villiger oxidation.

Table 19. Baeyer-Villiger oxidation of a range of electron deficient α,β -unsaturated methyl ketones with *m*CPBA.

				
Entry	α,β -Unsaturated ketone	Vinyl Ester	Catalyst	Yield
1	 398	 418	DMAP	55
2	 399	 419	DMAP	53
3	 395	 420	-	35 ^a
4	 400	 421	-	45

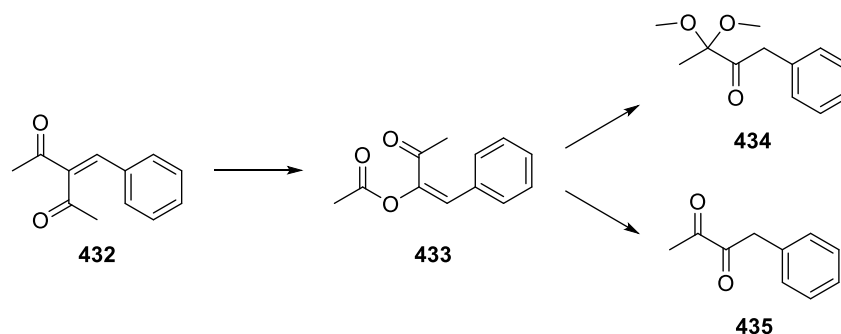
^a1mmol scale.

The developed methodology therefore tolerates a wide range of functional groups, including halogen, ester and ether substituents. Potentially oxidisable functionalities, such as a furyl ring, were also amenable to the oxidation conditions as were substrates of varying substitution patterns about the vinyl and aromatic moieties. The slight discrepancy observed between the measured

conversions and isolated yields may be attributable to instability of the vinyl esters on the acidic silica column. It is noteworthy that many of the vinyl esters and by-products isolated as analytically pure samples were found to be relatively unstable when left at room temperature for an extended period of time; degrading to numerous unidentified species. Therefore, timely use or storage at lower temperatures under anhydrous conditions is advisable.

2.3.6.2 Oxidation of 3-benzylidene-2,4-pentanedione

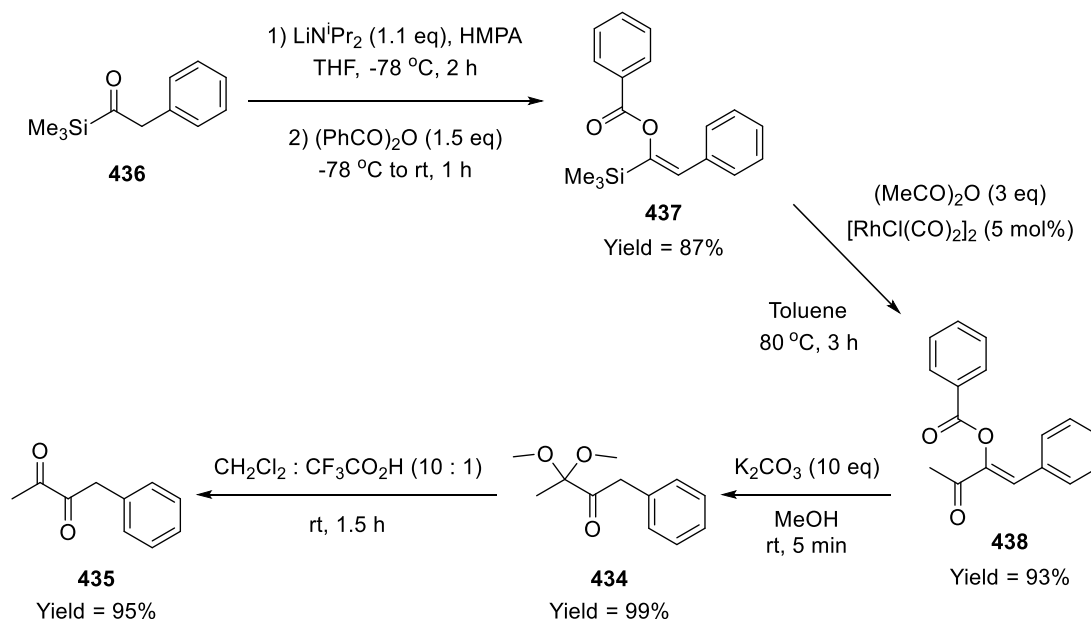
To demonstrate the synthetic utility of the devised oxidation protocol, the synthesis of α -acetoxy enone **433** was attempted (Scheme 199). Due to the moderately electron withdrawing ketone substituent on the α -carbon, which would destabilise the forming positive charge, it was anticipated that the oxidation of **432** would proceed with rate-determining migration. Although it was thought that the reaction would not be susceptible to catalysis by DMAP, the trisubstituted vinyl ester **433** was of particular interest. As well as being a novel compound, α -acetoxy enone **433** is a precursor to α,α -dialkoxy ketone **434** and α -diketone **435**.



Scheme 199. Application of the Baeyer-Villiger oxidation protocol to the multi-step synthesis of α,α -dialkoxy ketone **434** and α -diketone **435**.

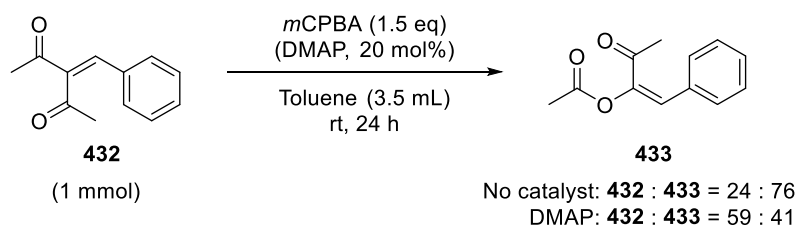
In 2005, Narasaka and co-workers reported that unsymmetrical diketones, which are important intermediates for the construction of heterocycles, could be prepared in five steps from acylsilane **436** via structurally related α -benzoxo enone **438** (Scheme 200).⁴⁵⁵ Initially, *O*-acylation of **436** via the corresponding lithium enolate generated **437**, which was subsequently treated with acetic anhydride in the presence of $[\text{RhCl}(\text{CO})_2]_2$ to afford α -benzoxo enone **438**.⁴⁵⁵ The authors were surprised to find that refluxing α -benzoxo enone **438** in 3M HCl did not result in deacylation to α -diketone **435**.⁴⁵⁵ Instead, using K_2CO_3 in MeOH furnished novel α,α -dialkoxy ketone **434** in 99% yield, which could undergo facile hydrolysis to the α -diketone **435** at room temperature under acidic conditions (1:10 trifluoroacetic acid:dichloromethane).⁴⁵⁵ Interestingly, this remains the only method for the preparation of **434** reported to date.⁴⁵⁵ Although each transformation was extremely high yielding, this multi-step method is particularly wasteful, time consuming and employs expensive reagents. Therefore, the aim was develop a more efficient and less wasteful

route for the synthesis of α,α -dialkoxy ketone **434** and α -diketone **435** from commercially available 3-benzylidene-2,4-pentanedione **432**.



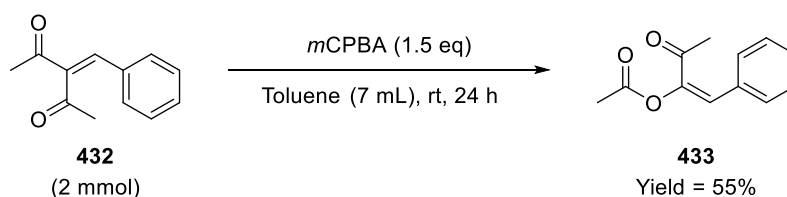
Scheme 200. Published method for the preparation of **434** and **435** from acylsilane **436**.⁴⁵⁵

As anticipated, DMAP exhibited no catalytic activity within the oxidation of **432**; implying that under these conditions the oxidation of this substrate proceeds with rate determining migration (Scheme 201). In actuality, DMAP inhibited the desired reaction and produced a larger number of unidentifiable by-products, as determined by ¹H NMR spectroscopic analysis of the crude reaction mixtures. Focussing on the ratio of the two major reaction components, conversion of the starting material was reduced from 76% to 41% by the addition of DMAP for oxidations conducted for 24 hours.



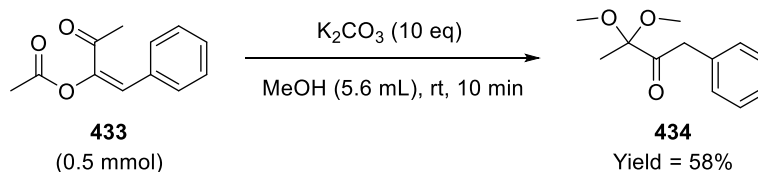
Scheme 201. Examining the catalytic potential of DMAP within the Baeyer-Villiger oxidation of **432**.

Subsequently, α -acetoxy enone **433** was successfully prepared in a moderate 55% isolated yield from the treatment of 3-benzylidene-2,4-pentanedione **432** with *m*CPBA (1.5 equiv.) in the absence of catalyst for 24 hours (Scheme 202). Notably, this method is operationally simple, as it does not require exclusion of air or moisture and the reaction is run at room temperature.



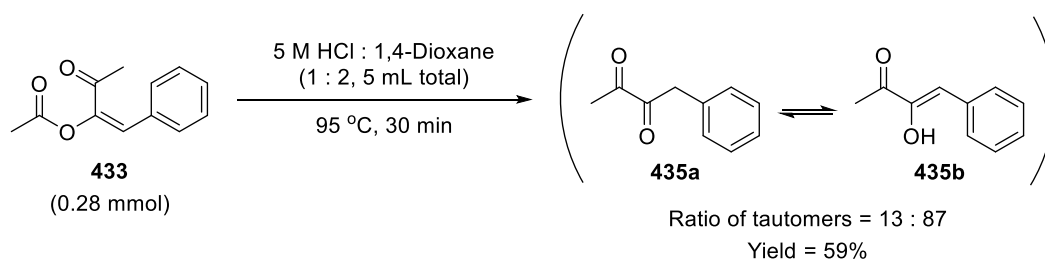
Scheme 202. *m*CPBA mediated oxidation of ketone **432** to vinyl ester **433**.

Using the conditions reported by Narasaka *et al.*,⁴⁵⁵ almost complete consumption (>95%) of the α -acetoxy enone **433** was observed after 10 minutes and pleasingly after an aqueous wash the major peaks within the ^1H NMR spectrum could be attributed to α,α -dialkoxy ketone **434** (Scheme 203). Unfortunately, the minor impurities were not removed on passing the crude reaction mixture through a Florisil[®] column and purification by silica gel column chromatography resulted in analytically pure material but eroded the yield, with α,α -dialkoxy ketone **434** isolated in a 58% yield.



Scheme 203. Preparation of α,α -dialkoxy ketone **434** from vinyl ester **433**.

Curiously, whilst α -benzoxo enone **438** was reported by Narasaka to be stable to deacylation under acidic conditions,⁴⁵⁵ direct deacetylation in this instance was achieved by refluxing α -acetoxy enone **433** in a 1:2 mixture of 5M HCl:1,4-dioxane for 30 minutes, according to a literature procedure (Scheme 204).⁴⁵⁶ α -Diketone **435** was obtained in a 59% yield after purification by column chromatography, although it should be noted that this isolation was performed on a 0.3 mmol scale. Interestingly, in deuterated chloroform the ketone **435a** and enol **435b** tautomeric forms were observed in a 13:87 ratio. Presumably an artefact of the impurities in the crude reaction mixture, the ratio of ketone:enol tautomer was measured as 29:71 prior to purification. This was determined by comparison of the integrals for the characteristic signals at 4.03 ppm and 6.44 ppm respectively within the ^1H NMR spectrum.^{457,458}



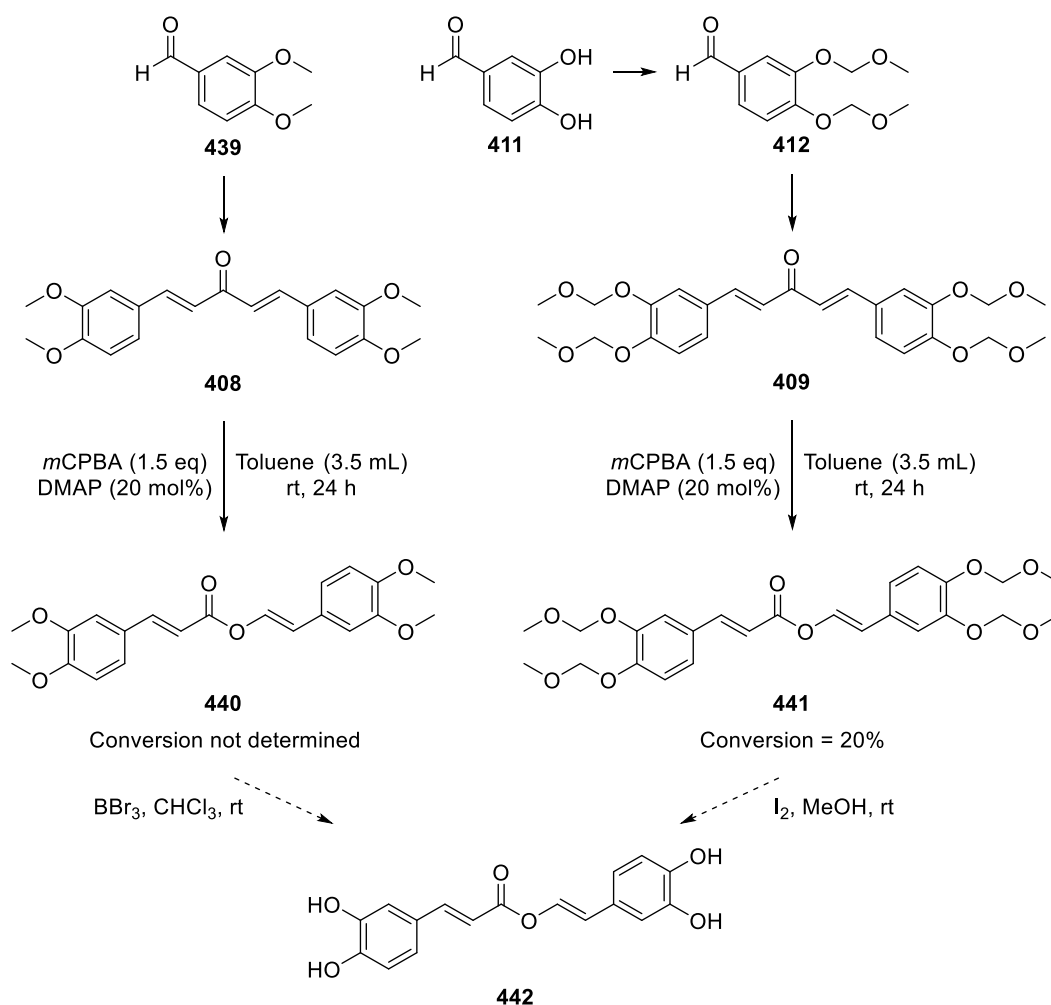
Scheme 204. Deacetylation of **433** to afford α -diketone **435**.

Thus, α,α -dialkoxy ketone **434** and α -diketone **435** can be accessed in moderate yield in only two steps from commercially available 3-benzylidene-2,4-pentanedione **432**. It is anticipated that optimisation of the isolation procedures and performing the reactions on a larger scale will allow for these yields to be greatly improved but this is beyond the scope of this work.

2.3.6.3 Baeyer-Villiger oxidation of chalcone derivatives

Based on the success of the developed methodology for the synthesis of vinyl acetates, we were interested in examining the oxidation of α,β -unsaturated ketones containing alternative substituents adjacent to the carbonyl. Aryl ketones and those with extended conjugation are less electrophilic.^{281,295,459,460} Therefore, it was reasoned that the oxidation of dibenzylideneacetone and chalcone derivatives, which are thought to be less reactive towards oxidation,^{228,281} may proceed with rate determining addition and thus be catalysed.

Initially, investigations were focussed on examining the suitability of the developed methodology for the synthesis of electron rich derivatives **440** and **441** (Scheme 205). As well as being interesting in their own right these species are potential precursors to ester **442**, which is a natural product known to exhibit biological activity.³⁴¹ It was hoped that the stereospecific oxidation of **408/409** followed by deprotection would provide a method for selectively preparing **442** as the (*E,E*)-diastereomer, which remains a synthetic challenge. Protection of the hydroxyl groups was deemed necessary based on the degradation observed for **431**.²⁹⁵ Both the methoxy and methoxymethyl acetal (MOM) functionalised dibenzylideneacetone derivatives **408** and **409** were synthesized *via* the base promoted aldol condensation of acetone with the appropriate disubstituted aromatic aldehyde (**439** or **412**), as detailed in section 2.3.5. Whilst 3,4-dimethoxybenzaldehyde (**439**) was commercially available, the MOM protecting groups of **412** were installed initially by treating 3,4-dihydroxybenzaldehyde (**411**) with diisopropylethylamine and bromomethyl methyl ether in the presence of catalytic quantities of DMAP.

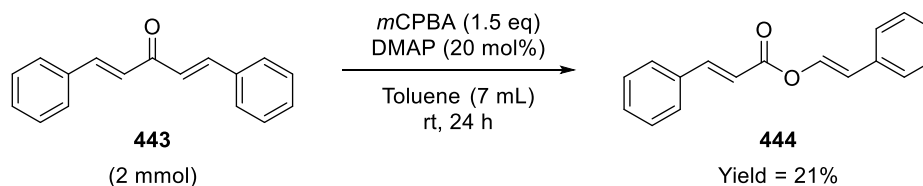


Scheme 205. Proposed synthetic route for the synthesis of natural product **442**.

With regards to the Baeyer-Villiger oxidation of these deactivated ketones, the MOM protected species (**409**) provided more promising results. In the presence of DMAP, 20% conversion of **409** into the corresponding ester **441** was observed after 24 hours, as determined by analysis of the ¹H NMR spectrum. However, further optimisation is required to develop a viable method, which may include examining peracids of greater oxidising ability, such as trifluoroperacetic acid. Applying DMAP to the oxidation of the methoxy analogue **408** provided a cleaner reaction profile relative to the background, however formation of the desired ester **440** was found to be minimal.

From investigations into the oxidation of methyl ketones, the activation energy barrier to addition for the uncatalysed reaction was found to increase with the electron donating capacity of the aryl substituent. Therefore, in combination with the extended conjugation, the ether functionality of **408** and **409** may be rendering the carbonyl carbon of these substrates less electrophilic due to increased electron density within the π -system. On the basis of this, it was reasoned that unfunctionalised dibenzylideneacetone (**443**) may be a more suitable substrate (Scheme 206). Pleasingly, the oxidation of **443** in the presence of DMAP proceeded with the formation of fewer

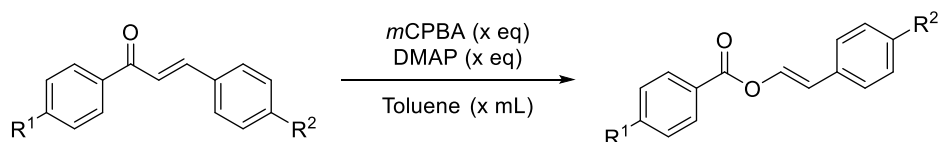
by-products and ester **444** was successfully isolated *via* column chromatography in 21% yield (Table 20, entry 8).



Scheme 206. Baeyer-Villiger oxidation of dibenzylidene acetone **443.**

Next, the oxidation of chalcone derivatives was examined. As a phenyl group is a moderately good migrating group (see migratory aptitude scale), it was hoped that by examining substituted chalcones the relative migratory aptitude of the vinyl group could be examined, whilst also allowing access to typically elusive ester products. Table 20 displays the aryl substituted ketones that were subjected to the Baeyer-Villiger methodology. Again, owing to the reduced reactivity of these ketones, the reactions were performed for 24 hours. Unfortunately, due to the complexity of the ^1H NMR spectra obtained for the crude reaction mixtures and the presence of overlapping peaks, accurate conversions could not be determined. Nevertheless, where characteristic peaks for the starting material and products were discernible, it was possible to qualitatively establish that most of the oxidations are catalysed in the presence of DMAP. Thus, it is reasoned that the uncatalysed oxidation for many of these chalcone derivatives proceeds with rate determining addition. Additionally, due to the extremely sluggish background rate, the catalytic effect of the DMAP additive was particularly evident for this substrate class. In some instances, such as the CF_3 substituted derivative **406**, considerable over-oxidation of the vinyl ester was limited and a cleaner reaction profile ensued (Table 20, entry 5).

In many instances large amounts of the starting material remained. Thus, several strategies were implemented in an attempt to increase the conversions achieved (Scheme 207). As previously observed for methyl ketones, higher catalyst loading (50%), dosing in additional catalyst and leaving the reaction for an extended period of time provided negligible improvement, with the reaction appearing to stall. Whilst in some cases a greater excess of *m*CPBA, either added initially (2.5 equiv.) or dosed in (1 equiv.), provided a slight improvement, for other substrates a more complicated mixture of reaction products was formed. Therefore, the previously optimised reaction conditions continued to be employed.

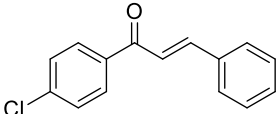
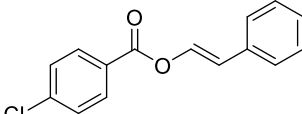
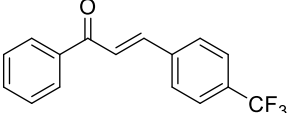
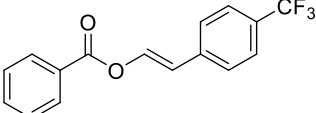
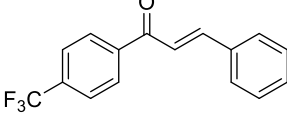
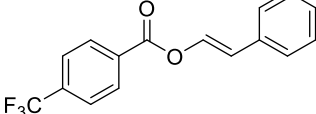
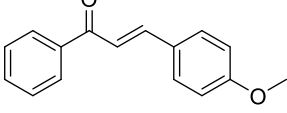
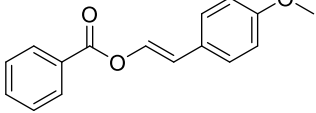
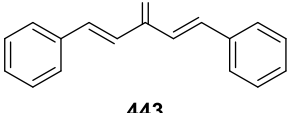
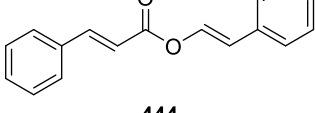


Scheme 207. Variation of reaction conditions for the oxidation of chalcone derivatives.

Although only low to moderate yields of the vinyl esters were isolated (15-54%), chalcone derivatives are anticipated to be relatively unreactive towards the Baeyer-Villiger oxidation.^{228,281,295,459,460} Furthermore, the developed methodology allowed access to functionalised derivatives **449**, **450** and **452** (Table 20, entries 2, 3 and 5), which are novel compounds. Chalcones in which the α -phenyl ring was furnished with electron withdrawing groups, such as Cl (**447**) or CF₃ (**407**), provided superior yields (Table 20, entries 4 and 6), which may be attributed to the more electropositive nature of the ketone. All esters were isolated as a single regioisomer, with oxygen insertion adjacent to the vinyl group, as determined by the deshielded aromatic signals within the ¹H NMR spectra. Therefore, it may be surmised that the relative migratory aptitude of a vinyl group is at least as good as a phenyl group.

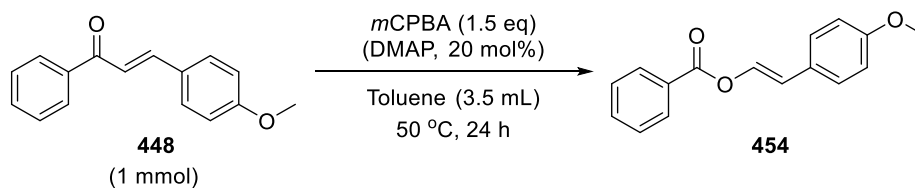
Table 20. Baeyer-Villiger oxidation of a range of chalcone derivatives with *m*CPBA in the presence of DMAP.

Entry	α,β -Unsaturated ketone	Vinyl ester	Yield (%)
1	<p>312</p>	<p>316</p>	43
2	<p>445</p>	<p>449</p>	45 ^a
3	<p>446</p>	<p>450</p>	41

4		44
	447	
		
	451	
5		26
	406	
		
	452	
6		54
	407	
		
	453	
7		15
	448	
		
	454	
8		21
	443	
		
	444	

^a0.4 mmol scale.

Chalcone derivatives are more poorly electrophilic due to the increased conjugation and presence of an α -aryl substituent.²²⁸ Although in many instances DMAP was found to promote the oxidation of functionalised chalcones, with minimal background reactions often observed, the reactions were found to be particularly sluggish and appeared to stall. In a further attempt to improve conversion, the oxidation of the *p*-methoxy derivative **448** was repeated at 50 °C (Scheme 208). Interestingly, essentially the same conversion was achieved; an observation also noted for other substrates. This finding is consistent with the proposal that the active catalyst promotes the reaction by participating in hydrogen bonding interactions. Although the enhanced temperature may promote the background reaction, it may also be expected to disrupt any hydrogen bonds formed.

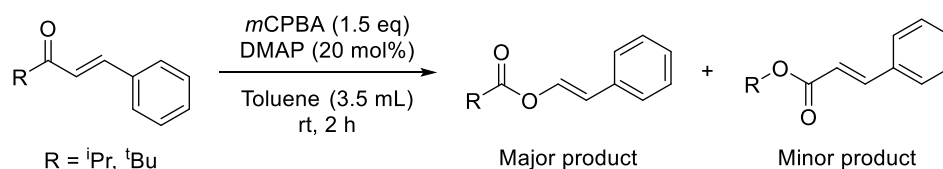


Scheme 208. Examining the effect of temperature on the extent of the Baeyer-Villiger oxidation of **448**.

2.3.6.4 Baeyer-Villiger oxidation of α,β -unsaturated alkyl ketones

It is generally accepted that the relative migratory aptitude of ketone substituents within the Baeyer-Villiger oxidation follows the sequence: tertiary alkyl > cyclohexyl > secondary alkyl > benzyl > phenyl > primary alkyl > cyclopentyl, cyclopropyl > methyl.²²⁸ Thus, alkyl groups feature at varying positions throughout this scale, with methyl and tertiary alkyl groups representing both extremes.²⁸¹ As substitution of the α -carbon increases, migration becomes progressively more facile due to increased stabilisation of the partial positive charge.^{232,233,242,277,291,294} Therefore, it was hoped that, by examining the regioselectivity achieved within the oxidation of α,β -unsaturated alkyl ketones of varying steric bulk, the relative migratory aptitude of the vinyl group under the developed reaction conditions may be established. As well as the importance of the corresponding vinyl esters, this would additionally provide an opportunity to examine the effect of steric bulk about the ketone on the rate of reaction.

With the exception of the α,β -unsaturated aldehyde (Table 21, entry 1), all reactions were accelerated in the presence of DMAP (Table 21). Therefore, it may be surmised that the uncatalysed oxidation of these α,β -unsaturated alkyl ketones proceeds with rate-determining addition of the peracid. It has also been determined that both the catalysed and uncatalysed oxidation of methyl, ethyl and phenyl substituted ketones are regioselective, with exclusive migration of the styryl moiety. However, whilst the vinyl ester remained the major product, a small amount of competitive alkyl migration was observed for the secondary and tertiary carbon centres of **404** and **405** (Scheme 209, Table 21, entries 4 and 5). Collectively, these findings indicate that under the developed reaction conditions the styryl fragment is a slightly better migrating group than a *tert*-butyl group, which appears at the top of the migratory aptitude scale (Figure 54).²²⁸ As such, regioselective oxidation adjacent to the vinyl group should be possible for the majority of ketones applied to this method. Intriguingly, competitive migration of the isopropyl group was only observed in the absence of catalyst.



Scheme 209. Regioisomeric products formed from the oxidation of ketones bearing ⁱPr and ^tBu groups.

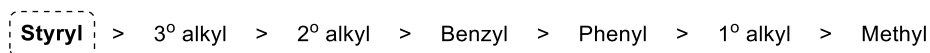
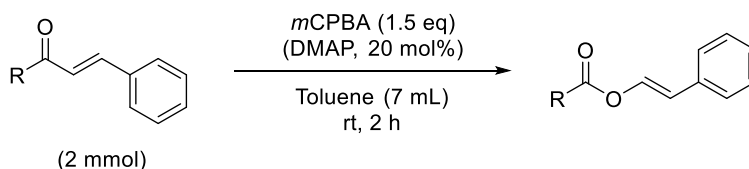


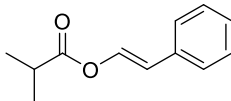
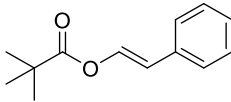
Figure 54. Predicted position of the styryl group within the migratory aptitude scale.²²⁸

With increasing steric bulk about the ketone, the rate of the uncatalysed reaction became progressively slower, with the *tert*-butyl ketone **405** failing to react at all (Table 21, entry 5). Alternatively, in the presence of DMAP the methyl, ethyl and isopropyl derivatives all achieved similarly high conversion and selectivity for the vinyl ester (77-79%, Table 21, entries 2-4). Most significantly, DMAP was found to promote the reaction of the sterically encumbered *tert*-butyl species **405** with some degree of regioselectivity (Table 21, entry 5). Improved conversion could not be achieved for the latter by extending the reaction time to 6 or 24 hours, with the reaction appearing to stall. The regioselectivity of the epoxides was determined by comparison of the characteristic peaks within the crude ¹H NMR with those reported within the literature.

Table 21. Examining the migratory aptitude within the Baeyer-Villiger oxidation of α,β -unsaturated alkyl ketones.



Entry	Vinyl Ester	Conditions	A	Ester ^b	B ^b	C	D	E ^c	F
1 ^a		-	3	66	16	13	-	n.d	-
		DMAP	14	75	2	-	-	n.d	-
2		-	28	30	16	13	6	4	3
		DMAP	6	79	14	-	-	-	1
3		-	51	20	18	1	2	3	5
		DMAP	7	77	13	1	-	-	2

4		-	76	9 (1)	8(1)	1	-	1	3
		DMAP	6	78	14	1	-	-	1
457									
5		-	100	-	-	-	-	-	-
		DMAP	40	36 (6)	14(2)	1	1	-	-
458									

Product ratios were determined by ^1H NMR spectroscopic analysis. ^aHydrolysis product also observed, No cat: 2%, DMAP: 9%. Small quantities of an unidentified acid or aldehyde also observed. ^bValues in parentheses indicate selectivity for alternative regioisomer involving migration of the alkyl group. ^cNot determined (n.d.).

Presumably due to the increased electrophilicity of an aldehyde relative to a ketone, the oxidation of *trans*-cinnamaldehyde (**459**) was not catalysed (Table 21, entry 1). However, improved selectivity for the corresponding vinyl formate **455** could be achieved in the presence of DMAP. Due to the complexity of the spectra and the presence of other formate based species, it was not possible to determine whether diformate **460**, generated from a second Baeyer-Villiger oxidation, had been formed (Figure 55). In contrast to the ketones examined, small amounts of the desired product were found to be hydrolysed to **340**; particularly in the presence of the catalyst. Leaving the catalysed reaction for an extended period of 6 hours resulted in oxidation of the aldehyde functionality to an acid, with additional doublets observed at 7.83 and 6.51 ppm ($J = 16.0$ Hz). Whilst the magnitude of the coupling constant is more consistent with the acid derived from the the starting material (**461**) rather than the formate product (**462**), the exact identity has not been unequivocally determined.

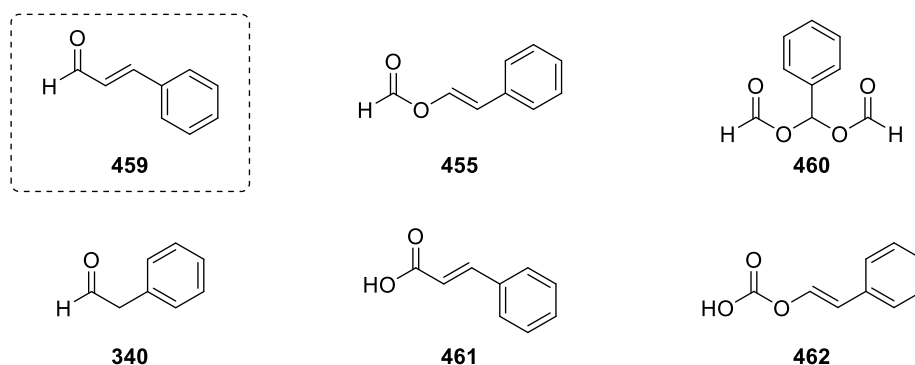
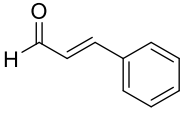
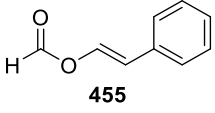
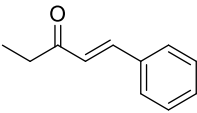
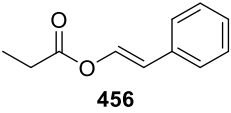
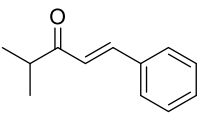
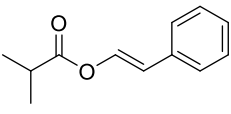
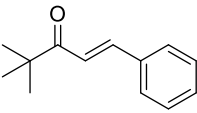
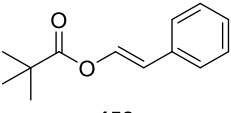


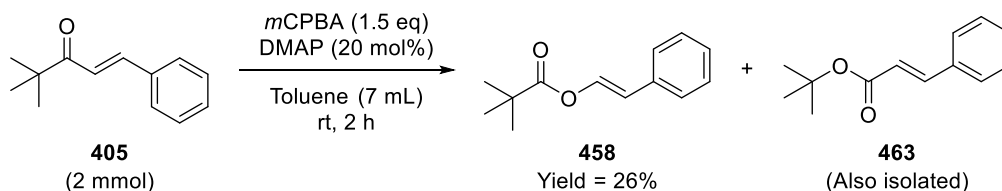
Figure 55. Potential products formed from the oxidation of *trans*-cinnamaldehyde (**459**).

Pleasingly, vinyl esters **456** and **457**, as well as vinyl formate **455**, were isolated in good yields following purification of the crude residues by flash column chromatography (Table 22, entries 1-3). Despite the particularly poor isolated yield of *tert*-butyl derivative **458** (Table 22, entry 4), achieving such a transformation demonstrates the synthetic importance of this methodology. This

is highlighted through the ability of DMAP to promote the oxidation of such a sterically encumbered ketone and the observed selectivity for vinyl group migration despite the exceptional migratory aptitude of a *tert*-butyl group. Small quantities of the regioisomeric vinyl ester **463** were also isolated, which was immediately identifiable by the downfield shift of the singlet attributable to the *tert*-butyl group within the ^1H NMR spectrum (Scheme 210).⁴⁶¹

Table 22. Baeyer-Villiger oxidation of a range of α,β -unsaturated alkyl ketones with *m*CPBA in the presence of DMAP.

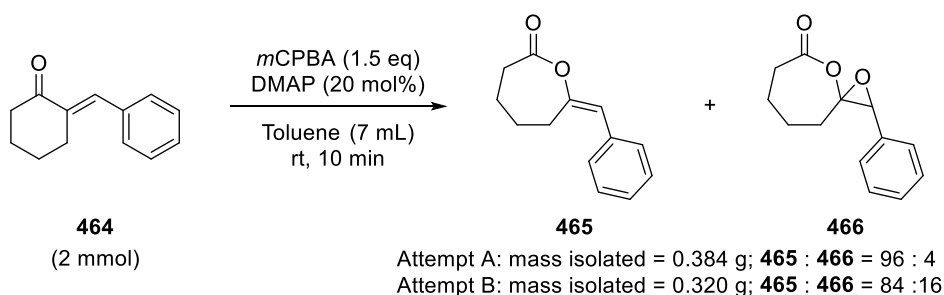
Entry	α,β -Unsaturated ketone	Vinyl Ester	Yield (%)
1	 459	 455	61
2	 403	 456	73
3	 404	 457	66
4	 405	 458	26



Scheme 210. Regioisomeric products isolated from the oxidation of **405**.

Owing to the success of acyclic alkyl ketones, the oxidation protocol was then applied to 2-benzylidenecyclohexan-1-one (**464**) (Scheme 211). In the absence of a catalyst, this cyclic

ketone undergoes particularly facile oxidation at both the carbonyl and alkene functionalities. Therefore, to allow for the effect of the catalyst on the reaction rate and product distribution to be examined, the reaction was performed for just 10 minutes. Notably, the product distribution in this instance was found to be particularly sensitive to the purity of the *m*CPBA reagent employed. Using a seemingly less active batch of *m*CPBA, reasonably large quantities of the starting material remained in the uncatalysed reaction, with small amounts of the epoxy ester already formed. Pleasingly, DMAP was found to accelerate the Baeyer-Villiger oxidation of **464**; providing complete consumption of the starting material with only 4% over oxidation to the epoxy ester **466** in this case. As deduced for many of the acyclic counterparts, the oxidation of **464** appears to proceed with rate-determining addition under the background conditions. Subsequent attempts to repeat the oxidation with a different batch of *m*CPBA, resulted in much higher levels of both the desired and undesired oxidation being promoted. Although complete consumption of the starting material was achieved without the need for a catalyst, the selectivity for vinyl ester **465** was improved from 64% to 84% in the presence of DMAP. From both catalysed attempts, **465** and **466** were isolated by column chromatography as an inseparable mixture, with a high mass of material obtained. Unfortunately, recrystallisation was also ineffective at separating these oxygen rich species.



Scheme 211. Baeyer-Villiger oxidation of 2-benzylidenecyclohexan-1-one (**464**).

Further substantiating the validity of this method for predicting the rate-determining step, the oxidation of α,β -unsaturated ketones bearing a primary alkyl group rather than an aryl substituent on the olefin moiety, such as **467** and **468**, were not found to be catalysed (Figure 56). In accordance with the results obtained for substrates containing a double bond furnished with electron deficient aromatics, this is indicative of migration representing the rate limiting step. Based on the reduced capacity of an alkyl substituent to stabilise the forming positive charge relative to a conjugated phenyl group, this outcome was anticipated and is entirely consistent with the electronic argument applied to electron deficient aromatic substituents. In these instances selectivity for the desired vinyl ester was not enhanced in the presence of DMAP.

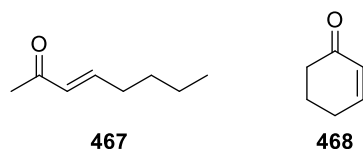
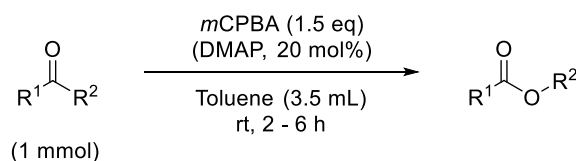


Figure 56. α,β -Unsaturated ketones bearing a primary alkyl group (**467** and **468**) which are not catalysed within the Baeyer-Villiger oxidation.

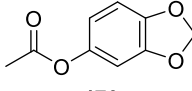
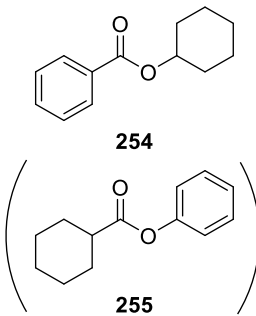
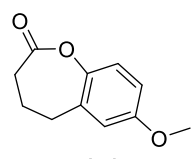
2.3.6.5 Baeyer-Villiger oxidation of saturated ketones

As DMAP was found to impart a catalytic effect within the oxidation of saturated substrates, such as *p*-methoxyacetophenone (**373**) and 3,3-dimethyl-2-butanone (**371**), the generality of this method for other saturated species was examined. Ketones were selected for this study based on the migratory ability of the substituent adjacent to the carbonyl, with good migrating groups targeted. Specifically, the oxidation of ketones bearing electron rich aryl groups or a cyclohexyl ring were investigated (Table 23). With the exception of 6-methoxy-1-tetralone (**472**) (Table 23, entry 5), all oxidations were catalysed in the presence of DMAP, with significantly higher conversion observed. It is postulated that this finding indicates that under the developed reaction conditions the uncatalysed oxidation of these species proceeds with rate determining addition. Alternatively, the lack of a catalytic effect within the oxidation of benzo-fused ketone **472** suggests that this reaction proceeds with rate-determining migration. This may potentially be the result of problems attaining the correct configuration for migration due to the constrained nature of the fused ring system. Nevertheless, it is noteworthy that in the absence of the catalyst 88% conversion into benzo-fused lactone **471** could be achieved in 24 hours (Scheme 212).

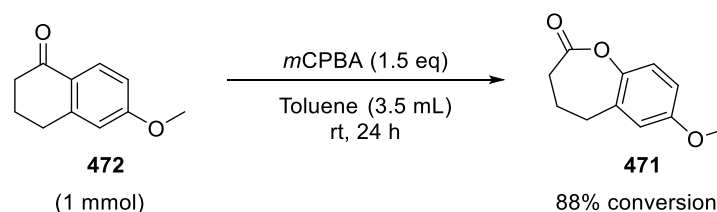
Table 23. Examining the Baeyer-Villiger oxidation of saturated ketones.



Entry	Vinyl Ester	Conditions	Ketone	Ester
1	 469	No cat, 2h	50	50
		DMAP, 2h	8	92
2	 377	No cat, 6h	91	9
		DMAP, 6h	24	76

3	 470	No cat, 6h	40	60
		DMAP, 6h	13	87
4	 254 255	No cat, 6h	93	7
		DMAP, 6h	34	61 (5)
5	 471	No cat, 6h	35	65
		DMAP, 6h	50	50

Conversions were determined by ^1H NMR spectroscopic analysis. Value in parentheses for regioisomeric ester corresponding to phenyl migration.



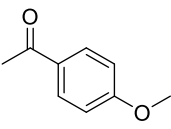
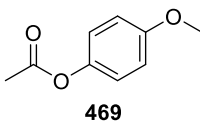
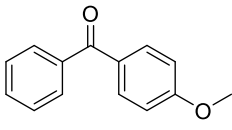
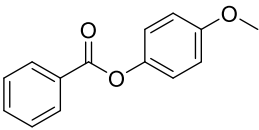
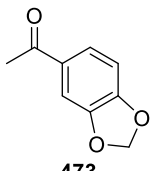
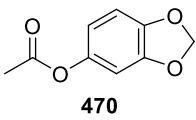
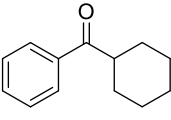
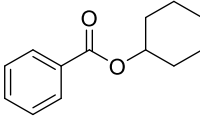
Scheme 212. Uncatalysed Baeyer-Villiger oxidation of fused ketone **472** to ester **471**.

As anticipated methyl ketones were found to be more reactive. Pleasingly, high conversion was achieved for the oxidation of methyl ketone **373** into the corresponding ester **469** after just two hours in the presence of DMAP (Table 23, entry 1), whilst the other species required a slightly extended reaction time of 6 hours (Table 23, entries 2-4). The rate enhancement is particularly obvious for the oxidation of less electrophilic diaryl ketone **376** into **377**,⁴⁶⁰ with 76% conversion observed in the catalysed reaction relative to a 9% background rate (Table 23, entry 2). Interestingly, a small amount of competitive migration was observed for the DMAP catalysed oxidation of cyclohexyl phenyl ketone (Table 23, entry 4). Regioisomers **254** and **255** were present within the ^1H NMR spectrum, as determined by comparison of the integrals for the triplet of triplets at 5.03 and 2.56 ppm respectively. Attempts to improve the conversions by leaving the reactions for an extended period of 24 hours were ineffective, with only a small increase in the extent of the background reaction observed. The identity of the peracid is known to influence the regiochemical outcome between such migrating groups, which are of similar migratory abilities.^{228,244,294} For instance, Hawthorne and co-workers reported that performing the oxidation

of cyclohexyl phenyl ketone with peroxyacetic acid provided a selectivity of 9:1 in favour of ester **254**, compared with a 4:1 ratio with the more reactive trifluoroperacetic acid.^{228,244,294}

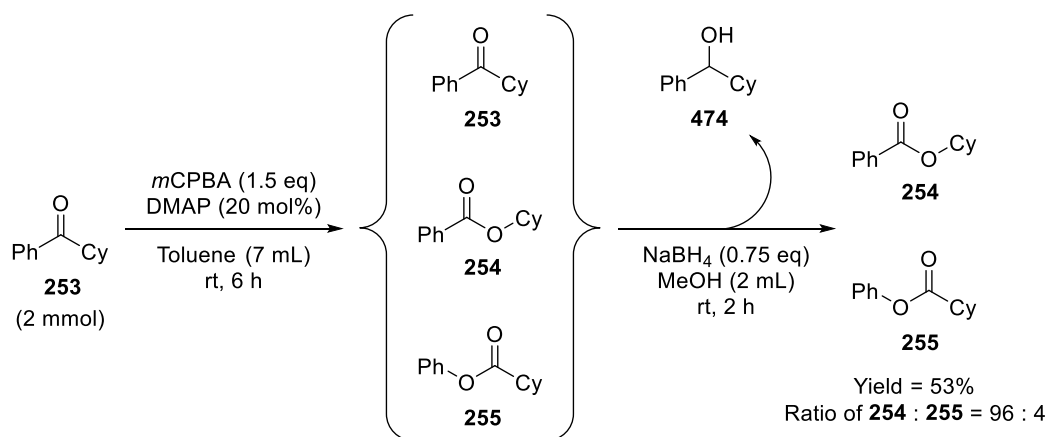
For the substrates that were found to be catalysed, the reactions were again scaled up and the corresponding saturated esters were purified and isolated by column chromatography in good yields (67-87%), with only relatively small losses encountered upon isolation (Table 24, entries 1-3). Unfortunately, purification by column chromatography or distillation proved unsuccessful at separating the cyclohexyl phenyl ketone **253** from the cyclohexyl ester products **254/255**, due to the similarity in the polarity and boiling point of these species (Table 24, entry 4). Thus, the ketone was selectively reduced to **474** with sodium borohydride and the ester was subsequently isolated *via* flash column chromatography in 53% yield, as a 96:4 mixture of regioisomeric products **254** and **255** (Scheme 213).⁴⁶²⁻⁴⁶⁴

Table 24. Baeyer-Villiger oxidation of saturated ketones with *m*CPBA in the presence of DMAP.

$ \begin{array}{ccc} \begin{array}{c} \text{O} \\ \parallel \\ \text{R}^1-\text{C}-\text{R}^2 \\ (2 \text{ mmol}) \end{array} & \xrightarrow[\text{Toluene (7 mL), rt, 2 - 6 h}]{\begin{array}{c} m\text{CPBA (1.5 eq)} \\ \text{DMAP (20 mol\%)} \end{array}} & \begin{array}{c} \text{O} \\ \parallel \\ \text{R}^1-\text{C}-\text{O}-\text{R}^2 \end{array} \end{array} $			
Entry	Ketone	Ester	Yield (%)
1	 373	 469	87 (2h)
2	 376	 377	67 (6h)
3	 473	 470	81 (6h)
4	 253	 254	53 (6h) ^a

^aYield obtained after reduction of the residual starting material with NaBH₄ and subsequent column chromatography. Only major regioisomer shown.

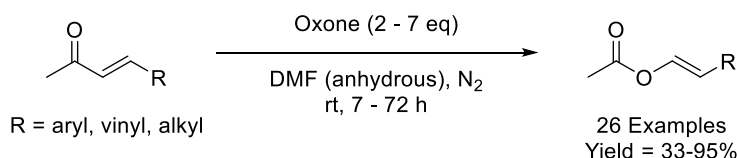
More specifically, cyclohexyl phenyl ketone (**253**) was initially subjected to the optimised oxidation conditions for 6 hours, with a mixture of the ketone (**253**) and ester products (**254/255**) obtained upon work-up (Scheme 213). Based on a literature procedure, the crude residue then was dissolved in methanol and treated with sodium borohydride for 2 hours at room temperature.⁴⁶⁵ After quenching with water, the desired product was extracted into ethyl acetate and purified by flash column chromatography.



Scheme 213. Selective reduction of unreacted ketone **253.**⁴⁶⁵

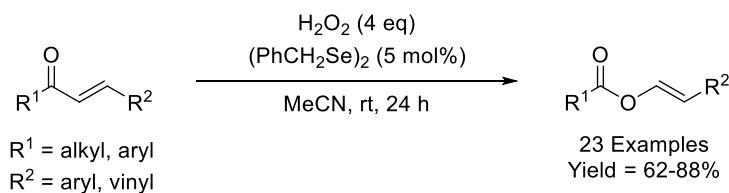
2.3.7 Comparison of literature methods

During the course of this work, del Amo *et al.* developed the first general method for the diastereoselective Baeyer-Villiger oxidation of α,β -unsaturated methyl ketones into (*E*)-vinyl acetates using Oxone[®] (potassium monopersulfate triple salt, KHSO₅•½KHSO₄•½K₂SO₄) (Scheme 214).³²⁸ Whilst a range of vinyl acetates were synthesized in moderate to excellent yields (R=Ar: 24 examples, 45-95%; R=aliphatic: 2 examples, 33-49%) and good functional group tolerance was reported, this method suffers from several limitations.³²⁸ For instance, the reported methodology is restricted to methyl unsaturated ketones, suffers from long reaction times (up to 72 hours), requires a large excess of Oxone[®] (2-7 equiv.) and requires inert conditions (dry DMF, N₂ atmosphere), which reduces its synthetic value.³²⁸ Additionally, the generality of the method is limited as reoptimisation, in terms of the amount of Oxone[®] and the reaction time, is required for each substrate to attain acceptable yields.³²⁸ Interestingly, during the optimisation studies *m*CPBA was identified as a more active oxidant than Oxone[®] in acetone.³²⁸ However, multiple reaction products were observed in the absence of a catalyst, which is in accordance with the findings of the work presented here.³²⁸



Scheme 214. Published procedure for the oxidation of α,β -unsaturated ketones with Oxone[®].³²⁸

Subsequently, in 2015 Xu, Yu and co-workers determined that recyclable dibenzyl diselenide (PhCH_2Se)₂ could promote the H_2O_2 mediated Baeyer-Villiger oxidation of α,β -unsaturated ketones to vinyl esters; allowing for the substrate scope to be expanded to ketones bearing more elaborate groups at the R^1 position (Scheme 215).³²⁹ Consistently good to excellent yields of the vinyl esters were afforded (62-88%), with the higher yields achieved for aromatics functionalised with electron donating groups.³²⁹ Crucially, substrates furnished with an electron withdrawing substituent on the R^1 aromatic were not amenable to oxidation and this method was not extended to substrates bearing a substituent more electron withdrawing than a halogen on the R^2 aromatic.³²⁹ Additionally, long reaction times of 24 hours and a large excess of the oxidant was required in all cases.³²⁹

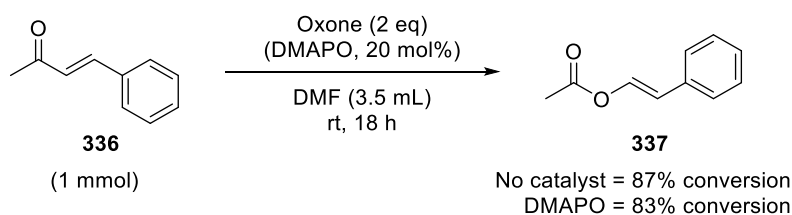


Scheme 215. Published procedure for the oxidation of α,β -unsaturated ketones with hydrogen peroxide.³²⁹

In contrast to these published methods, the developed *m*CPBA protocol appears to have a higher oxidising capability, facilitating its extension to electron deficient chalcones; albeit in low to moderate yield. As this method allows access to both vinyl acetates and vinyl benzoates of varying electronic demands, it may be considered complimentary to the procedures currently published. For the majority of substrates examined the reaction times have been greatly reduced (*cf.* parent substrate **337**: 2 hours *vs* 24 hours published). Additionally, the developed methodology allows for inert conditions to be circumvented and pleasingly requires much reduced concentrations of the oxidant (1.5 equiv.). More significantly, the DMAP derived catalyst provides a unique and powerful tool for examining the rate-determining step of a particular substrate under the reaction conditions (*m*CPBA oxidation in toluene), which has not been established previously for any of the aforementioned systems. Interestingly, the catalysed procedure is amenable to the oxidation of both unsaturated and saturated ketones proceeding with rate-determining addition, whilst in some instances the uncatalysed system is applicable to sluggish, electron poor substrates that exhibit rate-determining migration. Consistent with both literature reports, preferential vinyl

group migration was primarily observed, affording a single regioisomeric product exclusively as the *E*-stereoisomer.

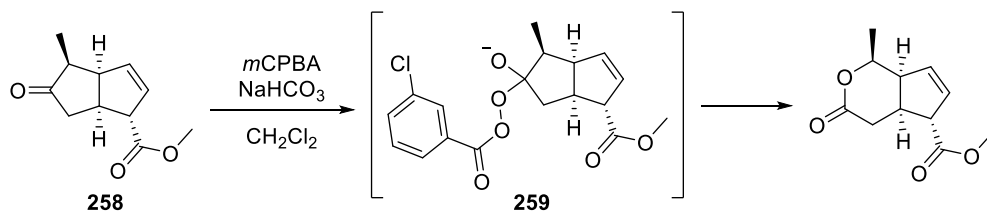
Following the reported success of Oxone[®] in DMF for achieving the Baeyer-Villiger oxidation of α,β -unsaturated methyl ketones,³²⁸ the potential catalytic effect of DMAPO within this system was explored (Scheme 216). As may be anticipated from the highly polar nature of the solvent, no enhancement in conversion was observed in the presence of DMAPO relative to the background reaction.



Scheme 216. Application of DMAPO to the Oxone[®] oxidation developed by Amo *et al.*³²⁸

2.3.8 Base and buffer promoted Baeyer-Villiger oxidations

The use of buffers and weak bases in the Baeyer-Villiger oxidation features heavily within the literature; particularly for oxidations performed with the more reactive peracid:acid combination to prevent acid catalysed side reactions occurring.^{238,242,268,272} Most commonly disodium hydrogen phosphate, sodium acetate and sodium bicarbonate are employed.²⁷² Interestingly, there are a small handful of examples where base catalysis has been observed.^{239,242,272,466} For instance, in 1978 Whitesell *et al.* reported that the rate of oxidation of bicyclic ketone **258**, performed using *m*CPBA in dichloromethane, was approximately doubled by the addition of heterogeneous bicarbonate (Scheme 217).^{228,268,309} It has been proposed that this rate enhancement arises from deprotonation of the hydroxyl moiety of the Criegee intermediate (**259**), which promotes the rearrangement step.^{228,268,272}



Scheme 217. Heterogeneous bicarbonate catalysed oxidation of **258** with *m*CPBA *via* the proposed deprotonated Criegee intermediate **259**.³⁰⁹

It has been suggested that based on the relative pK_a values of peracids and sodium bicarbonate, deprotonation of *m*CPBA to generate a more nucleophilic species is highly unlikely.²²⁸ However, it has been proposed that sodium bicarbonate deprotonates the *m*CBA by-product resulting in its

precipitation; thus preventing competitive reaction with the substrate to form adduct **475** (Figure 57).^{228,268} It is of particular significance that the rate of *m*CPBA oxidations is only accelerated by sodium bicarbonate when performed in non-hydrogen bonding solvents, such as chloroform and dichloromethane.^{228,309}

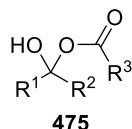


Figure 57. Proposed carboxylic acid adduct.²²⁸

As previously detailed, numerous theoretical and experimental studies have found that the rate of the Baeyer-Villiger oxidation performed in such non-polar solvents is enhanced in the presence of acid, with carboxylic acids operating as bifunctional catalysts (Figure 58).^{227,230-233,244,281,290,292,296,326,327} In some instances a hydrogen bonded complex (**263**) is even formed between the acid and ketone prior to reaction with the peracid.^{232,280,281,291,326,327} Therefore, it was considered that formation of adduct **475** and precipitation of the conjugate base of the acid catalyst would result in less favourable reaction kinetics, leading us to reason that these processes can be discounted. Also consistent with acid catalysis, during the course of our investigations the oxidations were often found to stall, which is thought to coincide with precipitation of the *m*CBA by-product.

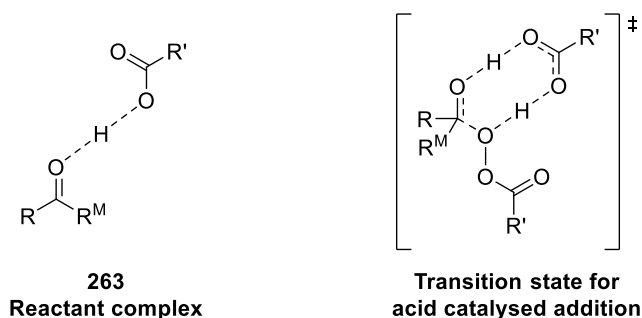


Figure 58. Proposed role of carboxylic acids within the addition step of the Baeyer-Villiger oxidation in non-polar solvents.^{230,327}

Computationally, it has also been determined that the lowest energy pathway for Baeyer-Villiger oxidations performed in non-polar solvents is concerted and entirely non-ionic, as charged species cannot be stabilised by solvation.^{244,280,291,296,321,326,327} Proton transfer between the general acid catalyst, substrate and peracid are therefore concerted and occur during the rate determining step.^{230,233,244,280,281,291,296,321,326,327} Based on these findings and the novel work presented herein, it may be hypothesised that the same mechanistic considerations can be extended to weak bases and that formation of the proposed anionic Criegee intermediate would be unfavourable. Therefore, it is speculated that sodium bicarbonate acts as a general base within the Baeyer-Villiger reaction

for oxidations performed with *m*CPBA in non-polar solvents. Specifically, the weak base facilitates proton transfer in the rate determining step; by extracting a proton from the peracid in the addition step and/or from the Criegee intermediate in the migration step (Figure 59). Concerted proton transfer is consistent with the solvent effects observed, as catalysis is only promoted in non-hydrogen bonding solvents.

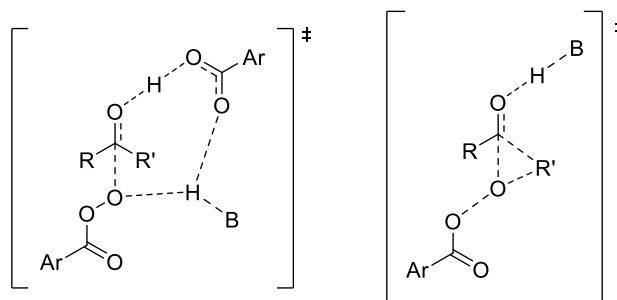
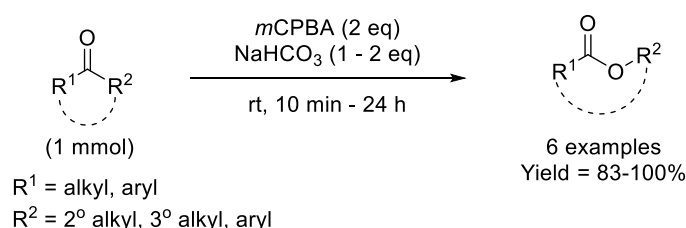


Figure 59. Potential roles of a general base within the Baeyer-Villiger oxidation.

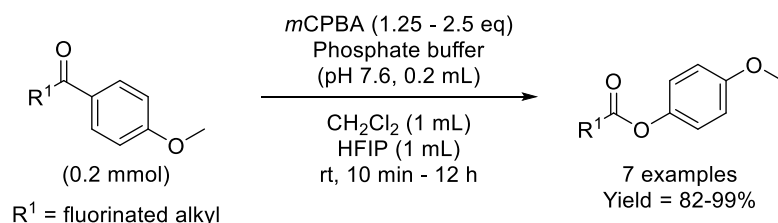
In 2002, the group of Uenishi developed a solvent-free, *m*CPBA oxidation of sterically encumbered ketones on the surface of NaHCO_3 , which allowed for numerous esters and lactones to be synthesized in high yields (83-100%) and in much reduced reaction times (Scheme 218).²³⁹ However, due to the solid state nature of the reaction and presumably the associated restricted diffusion, after 3 hours the reaction rate was found to drop off significantly.²³⁹ This could be overcome by addition and instant evaporation of dichloromethane every 3 hours.²³⁹ Although the authors do not speculate on the role of the bicarbonate catalyst, the low reactivity of the sterically encumbered ketones in the absence of base and in dichloromethane was ascribed to the bulky groups blocking both carbonyl faces, which hindered nucleophilic attack by the peracid.²³⁹ Therefore, we tentatively propose that these oxidations also involve general base catalysed addition.



Scheme 218. *m*CPBA oxidation of sterically congested ketones on the surface of NaHCO_3 .²³⁹

More recently, Uneyama *et al.* reported that the yield of α -fluorinated esters, obtained from the Baeyer-Villiger oxidation of α -fluorinated ketones with *m*CPBA, was altered depending on the identity of the solvent and the base.⁴⁶⁶ The most effective system identified was a weakly basic biphasic solution of aqueous phosphate buffer (KH_2PO_4 - NaOH , pH 7.6) in a 1:1 mixture of

1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) and dichloromethane (Scheme 219).⁴⁶⁶ The authors proposed that the components of the phosphate buffer, present in catalytic quantities (10 mol% KH_2PO_4 and 10 mol% NaOH), were responsible for the observed catalysis; with the aqueous base generating an anionic Criegee adduct, which enhances the rate of rearrangement.⁴⁶⁶ Interestingly, increasing levels of α -fluorination correlated with a sizeable increase in reactivity and yield (Table 25, e.g. entries 1, 6-9).⁴⁶⁶ As the carbonyl stretch shifted to higher wavenumber in the IR spectra with increasing fluorine incorporation, it was inferred that the observed reactivity trend could be attributed to electrophilic activation of the ketone (Table 26, e.g. row 3).⁴⁶⁶ However, these effects are contradictory. Unless there is a change in rate determining step, the base catalysis (proposed to catalyse rearrangement) and the enhanced rate with an increasing number of α -fluorine atoms (proposed to catalyse addition) are considered mutually exclusive for a particular compound.⁴⁶⁶ Typically, the rate of reaction is influenced only by the factors that reduce the activation energy for the rate-determining step.



Scheme 219. Base promoted Baeyer-Villiger oxidation of α -fluorinated ketones with *m*CPBA.⁴⁶⁶

Whilst the increased reactivity of ketones bearing α -fluorine atoms has been rationalised by an increase in the electrophilicity of the ketone, as determined by the higher wavenumbers in the IR spectra, this does not account for the decrease in reactivity observed for ketones bearing less electron donating substituents (Table 25, entries 4, 5 and 11).⁴⁶⁶ These compounds exhibit even higher carbonyl stretching frequencies and therefore by the same logic should be the most reactive (Table 26, row 4 and 5).⁴⁶⁶ Notably, if the reaction is acid catalysed, the extent of electrophilic activation of the carbonyl *via* proton transfer will not be reflected in the IR stretching frequencies.⁴⁶⁶ Also of particular interest, *p*-methoxyacetophenone was significantly more reactive than acetophenone towards oxidation (Table 25, entries 8-10).⁴⁶⁶ It is feasible that this rate enhancement is attributed to a more facile addition, as described, however it is known that the electron releasing properties of a substituent exerts a greater effect on the migration step.^{227,232,291,326}

Table 25. Effect of the ketone substituents on the rate and yield of the Baeyer-Villiger oxidation reported by Uneyama *et al.*⁴⁶⁶

$ \begin{array}{ccc} \text{R}^1-\text{C}(=\text{O})-\text{R}^2 & \xrightarrow[\text{rt, 10 min - 3 h}]{\begin{array}{l} m\text{CPBA (1.25 eq)} \\ \text{Phosphate buffer (pH 7.6, 0.2 mL)} \\ \text{CH}_2\text{Cl}_2 \text{ (0.5 mL)} \\ \text{HFIP (0.5 mL)} \end{array}} & \text{R}^1-\text{C}(=\text{O})-\text{O}-\text{R}^2 \\ (0.2 \text{ mmol}) & & \end{array} $				
Entry	R ¹	R ²	Time	Yield (%) ^a
1	CF ₃	Ph	10 min	87
2	CF ₃	4-MeO-C ₆ H ₄	10 min	>99
3	CF ₃	4-Me-C ₆ H ₄	10 min	95
4	CF ₃	4-Cl-C ₆ H ₄	10 min	76
5	CF ₃	<i>n</i> -C ₆ H ₁₃	10 min	57
6	CF ₂ H	Ph	10 min	48
7	CFH ₂	Ph	10 min	25
8	CH ₃	Ph	10 min	6
9	CH ₃	Ph	3 h	20
10	CH ₃	4-MeO-C ₆ H ₄	10 min	>98
11	CH ₃	<i>n</i> -C ₆ H ₁₃	10 min	4

^aDetermined by NMR spectroscopic analysis.

Table 26. IR carbonyl stretching frequencies for the ketones displayed in Table 25, with yields of the corresponding esters after 10 minutes shown in parentheses.⁴⁶⁶

Entry	R ¹ COR ²	CF ₃	CF ₂ H	CFH ₂	CH ₃	CF ₃ CF ₂
1	4-MeO-C ₆ H ₄	1707 [>99]	1698 [97]		1676 [>98]	1698 [94]
2	4-Me-C ₆ H ₄	1716 [95]				
3	C ₆ H ₅	1719 [87]	1712 [48]	1705 [25]	1683 [6]	
4	4-Cl-C ₆ H ₄	1722 [76]				
5	<i>n</i> -C ₆ H ₁₃	1765 [57]			1722 [4]	

In accordance with our own work and previous findings within the literature, one possible explanation that accounts for these discrepancies is a mechanism involving rate-determining migration for all substrates except *p*-methoxyacetophenone. For instance, the substantial difference in reactivity between *p*-methoxyacetophenone and acetophenone can be accounted for by general base catalysed addition of the former only. Additionally, the decrease in reactivity on descending each column (Table 26) may be rationalised by the progressively poorer migratory aptitude of each group. Nevertheless, it is more difficult to explain how α -fluorine incorporation may enhance the rate of migration.

Whilst isolated reports of base-catalysed Baeyer-Villiger oxidations exist, the role of the base has not yet been extensively investigated and in some instances is required in stoichiometric quantities.^{239,309,466} The mechanism proposed by Krow, which proceeds *via* a deprotonated Criegee intermediate, still remains generally accepted and unchallenged.²⁷² However, this process involves specific base catalysis, for which deprotonation is complete prior to the rate determining

step, and would not be expected for weakly basic species particularly in non-polar solvents. To the best of our knowledge, a general base catalysed addition step has not been postulated for the oxidation of ketones. However, a series of insightful but slightly overlooked publications by Ogata and Sawaki between 1969 and 1971 detail general base catalysis within the perbenzoic oxidation of benzaldehyde derivatives under acidic reaction conditions in both non-polar and polar solvents.^{297,434,467} The inclusion of small quantities of a general base, such as sodium acetate, in low concentration (as low as 0.002 M) was found to result in a marked increase in reaction rate.^{297,434,467} Interestingly, the authors noted some degradation of the peracid in the presence of basic species.^{297,434,467}

Therefore, we propose that weakly basic species may universally promote the addition step of the Baeyer-Villiger oxidation with peracids in non-polar solvents by functioning as general base catalysts; facilitating concerted proton transfer (Figure 60). The general base may be involved in proton transfer events in the transition state for either step but, as seen for the analogous acid catalysed systems, may be expected to exhibit a more pronounced effect for the addition step. For rate determining addition, the general base catalyst would be expected to function by aiding removal of the peracid proton in the transition state, which consequently enhances the nucleophilicity of this oxidising reagent, as described by Ogata and Sawaki.⁴³⁴ Interestingly, the authors also speculated that stronger bases and more acidic peracids should increase the degree of proton transfer achieved, thus further accelerating the oxidation.⁴³⁴ Notably, literature precedent exists for peracids participating in such intermolecular hydrogen bonds.^{434,468}

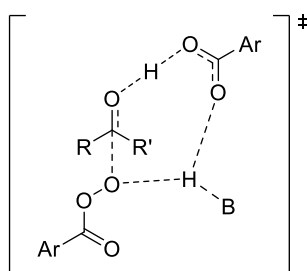
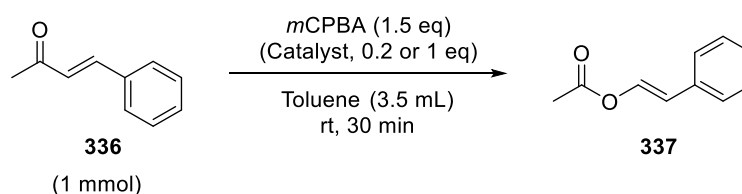


Figure 60. Proposed transition state for a general base catalysed addition step.

For the developed methodology, the organic *N*-oxide is thought to be functioning as a general base *via* hydrogen bonding interactions to facilitate concerted proton transfer within the addition step. Therefore, to determine whether inorganic bases, such as those reported within the literature, are capable of functioning in a similar manner, a range of basic species were applied to the optimised system. Successful extension to other weak bases would allow for the range of potential catalysts to be expanded and would also help substantiate the proposed role of the *N*-oxide.

Due to the success of numerous buffers within Baeyer-Villiger oxidations using peracids and the potential for the formation of sodium *m*-chlorobenzoate in the DMAP catalysed system, commercially available sodium benzoate was employed as an additive. Additionally, sodium bicarbonate, which has previously been reported to catalyse such Baeyer-Villiger oxidations, was also examined in this role. As can be determined from the results in Table 27, when employed in catalytic quantities, both sodium benzoate and sodium bicarbonate exhibit comparable catalytic activity to DMAP; albeit with slightly greater over-oxidation observed (Table 27, entries 2, 4 and 6). Interestingly, employing these bases in stoichiometric quantities resulted in reduced conversion and selectivity for the desired vinyl ester (Table 27, entries 5 and 7); a trend also observed for DMAP and DMAPO.

Table 27. Investigating the effect of basic additives on the Baeyer-Villiger oxidation of (*E*)-4-phenyl-3-buten-2-one (336) with *m*CPBA.



Entry	Catalyst	Ket. 336	Ester 337	Epox. 339	Ald. 341	Acid 353	Form. 354	Epox. 338
1	-	39	26	24	1	3	3	4
2	DMAP	3	74	18	2	1	-	2
3	DMAPO	8	73	17	-	-	-	2
4	Sodium benzoate	4	64	14	13	1	2	2
5	Sodium benzoate (1 equiv.)	33	50	12	-	1	-	4
6	Sodium bicarb	1	63	15	15	1	2	3
7	Sodium bicarb (1 equiv.)	5	56	32	2	1	2	2

Product ratios were determined by ^1H NMR spectroscopic analysis.

According to Laurence's hydrogen bond basicity database, carboxylates are very strong hydrogen bond acceptors ($\text{p}K_{\text{BHX}} > 3$).^{393,394} For instance, ammonium acetate has a $\text{p}K_{\text{BHX}}$ of 5.60, which is of similar magnitude to trimethylamine *N*-oxide, which exhibits a $\text{p}K_{\text{BHX}}$ of 5.46.^{393,394} Therefore, it is proposed that the *N*-oxide and carboxylate species may adopt the same role of facilitating proton transfer from the peracid in the rate-determining addition step (Figure 61). As previously detailed, it is plausible that an ammonium carboxylate species may form between DMAP and *m*-chlorobenzoic acid ($\text{p}K_{\text{aH}}$ DMAP = 9.58, $\text{p}K_{\text{a}}$ *m*CBA = 3.84)^{392,393} and therefore the carboxylate

may represent the general base within this reaction. Alternatively, the formation of a carboxylate in the presence of preformed DMAPO is considered unlikely based on the similarity of the pK_a values attributed to these species in water (DMAPO $pK_{aH} = 3.88$, *mCBA* $pK_a = 3.84$).^{392,417} Additionally, regardless of the protonated species ($COOH$ or $N^+ \rightarrow OH$), this system will still be comprised of an exceptional hydrogen bond acceptor and donor. It remains undetermined whether formation of the ammonium carboxylate salt or aromatic *N*-oxide from DMAP is more rapid under the reaction conditions and therefore which represents the catalytically active species within the optimised system. Nevertheless, the active species appears to be acting as a general base in the presence of a general acid (*mCBA*).

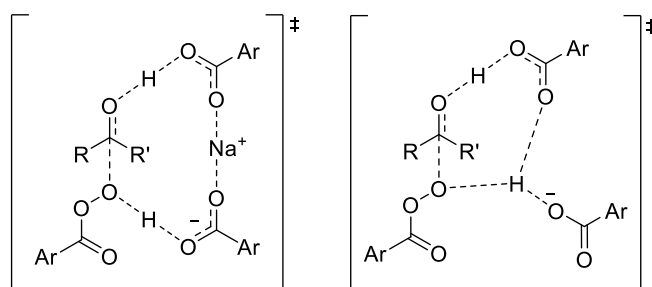
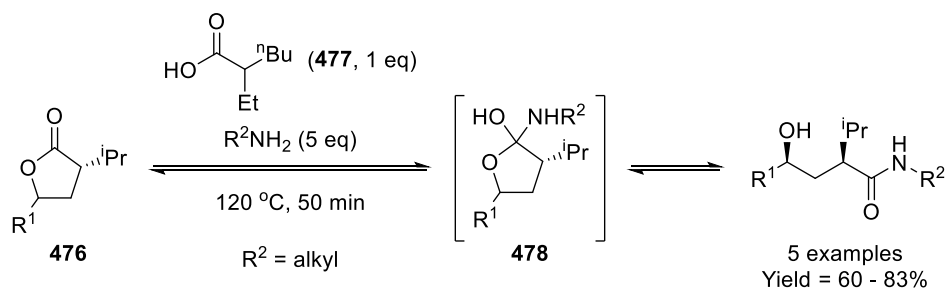


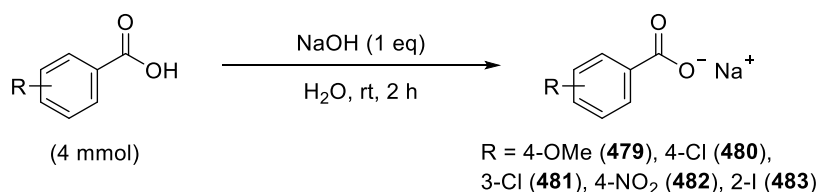
Figure 61. Proposed transition states for a carboxylate catalysed addition step.

Literature precedent exists for the application of carboxylates as general base catalysts.⁴⁶⁹⁻⁴⁷² Of particular relevance to this work is the ability of ammonium carboxylate salts to function cooperatively as general acid and general base catalysts within the aminolysis of lactones (**476**), as demonstrated by Jamison and Foley (Scheme 220).⁴⁶⁹ In this instance the stoichiometric catalyst was generated *in situ* from the amine reagent and 2-ethylhexanoic acid (**477**), although comparable results could also be achieved when employing the preformed salt.⁴⁶⁹ From extensive mechanistic studies, the authors speculate that within this acid promoted reaction the carboxylate functions as a general base to promote a kinetically significant proton transfer event during the formation of intermediate **478**.⁴⁶⁹ Significantly, ammonium salts containing alternative anions gave inferior results.⁴⁶⁹



Scheme 220. Ammonium carboxylate catalysed aminolysis of lactones.⁴⁶⁹

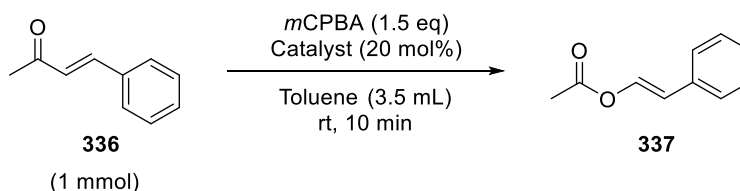
To examine the effect of the basicity of the benzoate catalyst on its activity, a series of sodium benzoate salts of varying pK_{aH} values were simply prepared and applied within the optimised Baeyer-Villiger methodology.³⁹² Specifically, this entailed treatment of the corresponding carboxylic acid in the minimum amount of water with sodium hydroxide, which was added portionwise to control the exotherm (Scheme 221). Once all of the solid had dissolved, the mixture was left to stir at room temperature for 2 hours. Azeotropic removal of the water with toluene *in vacuo* then afforded cleanly the desired salt. The absence of an OH peak/stretch within the ^1H NMR and IR spectrum coupled with a shift in the characteristic carbonyl stretch to much lower wavenumber within the latter were used for confirmation of successful salt formation.



Scheme 221. Preparation of sodium carboxylates.

Applying these substituted sodium benzoates in catalytic quantities (20 mol%) within the Baeyer-Villiger oxidation of **336**, highlighted no obvious correlation between the extent of oxidation and the pK_a of the conjugate carboxylic acid (Table 28). However, the salt of the most acidic species, 2-iodobenzoate (**483**), exhibited the lowest catalytic activity of any derivative examined (Table 28, entry 6). As the oxidation has been found to be particularly rapid even in the absence of any catalyst and only a small scope of benzoates within a narrow range of pK_{aH} values were employed, more instructive results may be obtained by repeating this study on a more sluggish substrate with benzoates of more disparate pK_a values. Nevertheless, these findings demonstrate the generality of the method with regard to the general base catalyst that may be successfully employed.

Table 28. Examining the effect of sodium carboxylates on the Baeyer-Villiger oxidation of (*E*)-4-phenyl-3-buten-2-one (336**).**

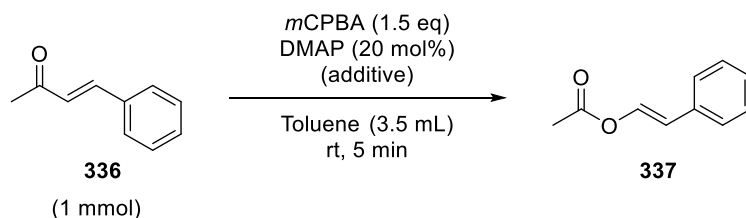


Entry	Catalyst	pK_{aH} ^{392,393}	Ketone 336	Ester 337	By-products
1	4-methoxybenzoate (479)	4.50	13	59	28
2	Sodium benzoate	4.20	18	62	20

3	4-chlorobenzoate (480)	4.00	17	55	28
4	3-chlorobenzoate (481)	3.84	13	63	24
5	4-Nitrobenzoate (482)	3.43	15	58	27
6	2-iodobenzoate (483)	2.86	22	57	21
7	DMAP	9.58	15	64	21

Product ratios were determined by ^1H NMR spectroscopic analysis.

It is proposed that under the optimised conditions the Baeyer-Villiger oxidation is both general acid and general base catalysed. Having examined the general base component in detail, attention was focussed on the general acid catalyst. It has been reported that the concentration of carboxylic acid present influences the reaction rate, with a discrepancy in activity noted between different preparations of the same peracid.^{228,323,326} Additionally, an autocatalytic effect has been reported, as the oxidation generates stoichiometric quantities of the carboxylic acid as a by-product.^{228,281,323,325} Therefore, benzoic acid (10 mol%) was employed as an additive in conjunction with DMAP (Scheme 222). Disappointingly, no improvement in conversion or selectivity was afforded beyond the use of DMAP alone. Similarly, employing diphenyl urea (20 mol%) as a co-catalyst, in an attempt to activate the ketone carbonyl again *via* hydrogen bonding interactions, did not provide any enhancement.

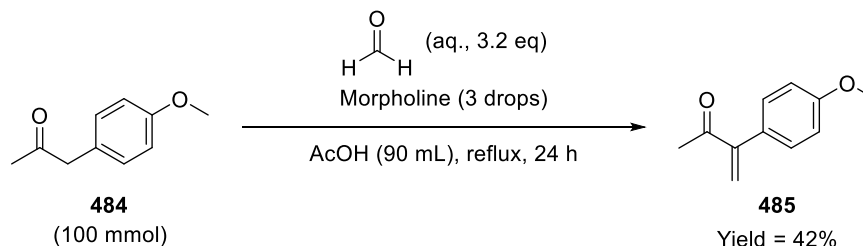


Scheme 222. Examining the effect of hydrogen bond donors on the Baeyer-Villiger oxidation of (*E*)-4-phenyl-3-buten-2-one (**336**).

2.3.9 Reactions of 3-(4-methoxyphenyl)but-3-en-2-one

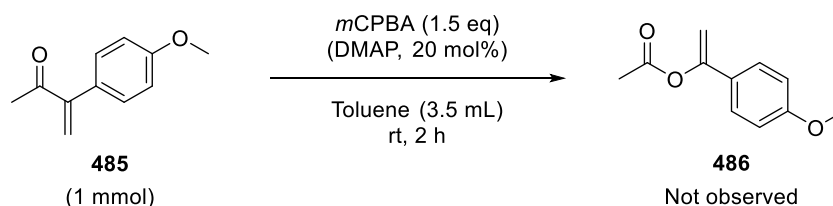
In a continuation of our studies into the substrate generality, we examined the tolerance of the reaction to other substitution patterns of the vinyl moiety. Specifically, the oxidation of α -methylene ketones presents an opportunity to access alk-1-en-2-yl acetates, which are useful enol intermediates.⁴⁷³ Thus, extension of the developed methodology to the synthesis of 1-(4-methoxyphenyl)ethenyl acetate (**486**) was of particular interest. In order to examine this substrate class, electron rich α -methylene ketone **485** was synthesized in 42% yield by the Mannich reaction of 4-methoxyphenylacetone **484** with formaldehyde, involving immediate elimination of morpholine from the *in situ* generated Mannich base (Scheme 223).^{474,475} The

reaction was conducted in glacial acetic acid at reflux for 24 hours, with the product subsequently purified by flash column chromatography.⁴⁷⁴



Scheme 223. Synthesis of 1-(4-methoxyphenyl)ethenyl acetate (**485**) from the Mannich reaction of **484** with formaldehyde.⁴⁷⁴

Application of the developed Baeyer-Villiger oxidation conditions to 3-(4-methoxyphenyl)but-3-en-2-one **485** for 2 hours, both in the presence and absence of catalyst, resulted in complete consumption of starting material, as determined by the absence of the distinctive peaks at 6.09 and 5.93 ppm within the ¹H NMR spectra.⁴⁷⁶ However, a complex mixture of reaction products ensued; none of which were the desired ester (**486**) or immediately identifiable by ¹H NMR spectroscopy (Scheme 224). TLC analysis also indicated the presence of multiple species. Repeating these reactions for an extended time of 6 hours did not appear to improve the selectivity for any particular compound; suggesting that these species may be formed *via* competing pathways. As slightly more discernible peaks were observed within the ¹H NMR spectrum for the uncatalysed reaction, this oxidation was repeated for 2 hours on a slightly larger 2 mmol scale and attempts were made to isolate and characterise the products.



Scheme 224. Attempted application of the optimised Baeyer-Villiger conditions to the oxidation of ketone **485**.

One of the major components from this reaction was successfully isolated by column chromatography (0.070 g). From spectroscopic analysis it was immediately discernible that this compound contained no carbonyl functionality. This was deduced from the absence of a characteristically strong C=O absorption signal within the IR spectrum and further supported by the absence of a resonance above 160 ppm within the ¹³C NMR spectrum. Additionally, analysis of the data indicated that the alkene functionality was no longer present. Instead, based on the unusual coupling observed for the inequivalent methylene protons and the presence of four distinct quaternary carbon centres within this high molecular weight species, it was considered

that dimerisation may have occurred. Recrystallisation of the solid from toluene at room temperature afforded colourless crystals suitable for single crystal X-ray diffraction analysis, from which the structure was unambiguously determined as the novel, oxygen rich, tricyclic cage compound **487** (Figure 62).

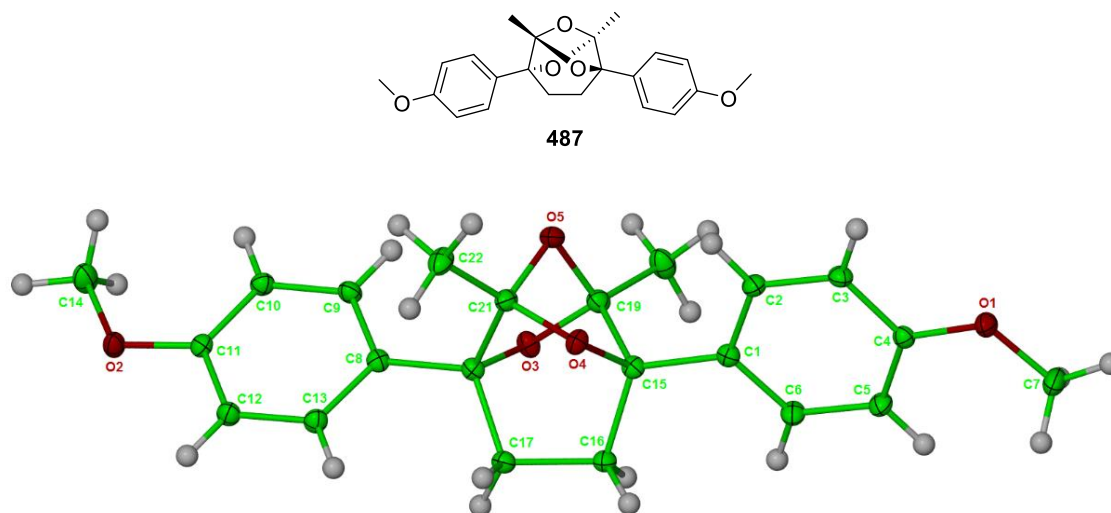
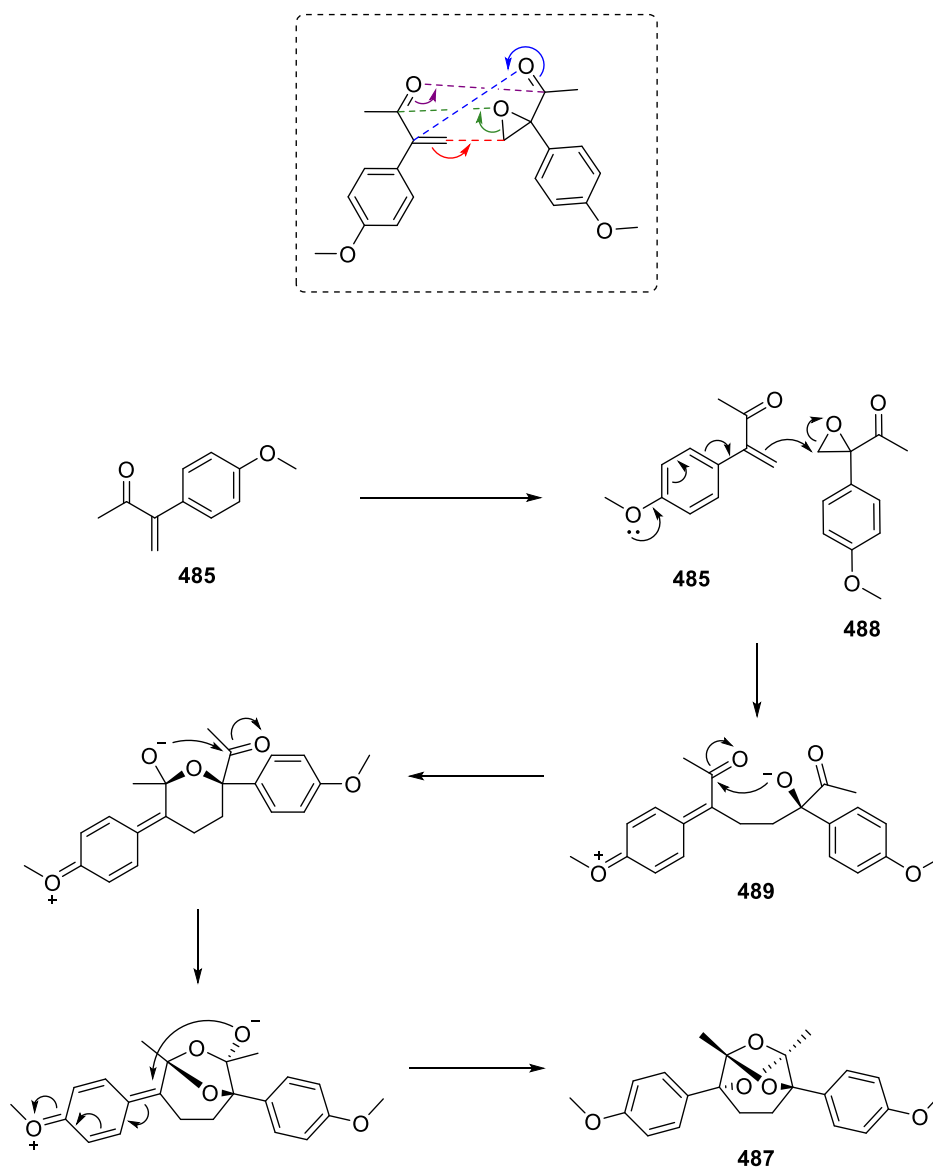


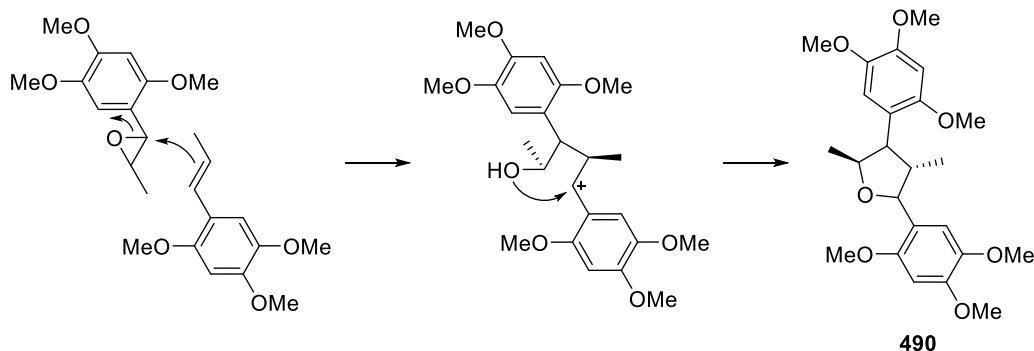
Figure 62. Crystal structure obtained for isolated oxygen-rich species **487**.

Initially, it was proposed that cage compound **487** was formed from the reaction of *in situ* generated epoxide **488** with 3-(4-methoxyphenyl)but-3-en-2-one **485** (Scheme 225). The double bond of **485** is much more nucleophilic than the internal alkenes studied previously, as the methoxy group donates electron density into the π -orbitals *via* resonance, and would therefore be expected to undergo more facile epoxidation with the electrophilic *m*CPBA oxidant. The electron rich double bond of the starting material (**485**) may then act as a nucleophile to ring open this derived epoxide (**488**) generating **489**, which for simplicity is shown as a stepwise process. Epoxide ring opening of this nature may be promoted under the acidic reaction conditions.



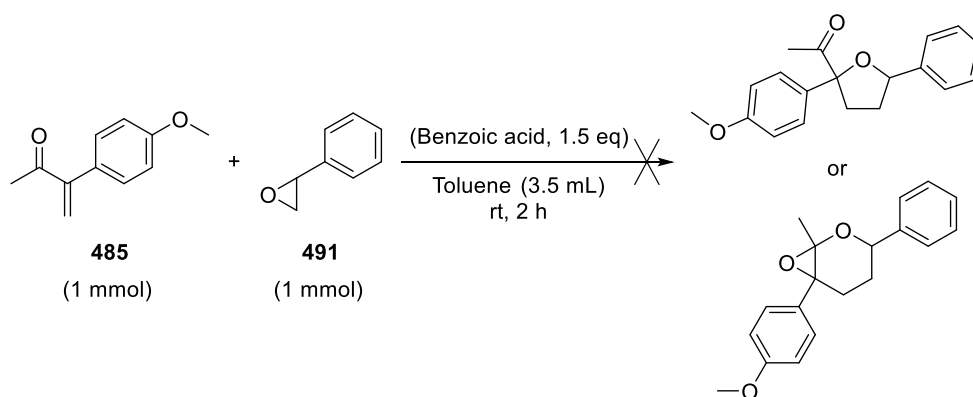
Scheme 225. Proposed mechanism for the formation of **487** from **485**.

Literature precedent exists to corroborate such a mechanism. For instance, Tsuruga *et al.* proposed that the biogenetic formation mechanism of magnosalicin **490**, which was successfully isolated from *Magnolia salicifolia*, involved ring opening of an epoxide by the electron rich parent alkene, as detailed in Scheme 226.⁴⁷⁷ However, it should be noted that in this instance nucleophilic attack occurs at the aryl substituted carbon of the epoxide.



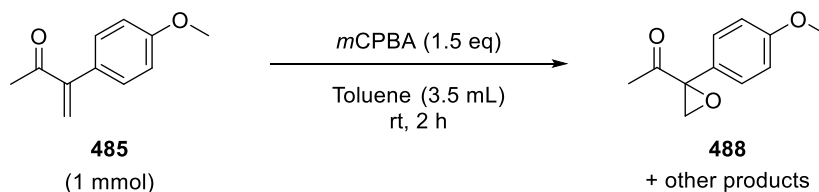
Scheme 226. Proposed mechanism for the formation of magnosalicin **490**.⁴⁷⁷

To examine the generality of this reaction and elucidate information on the mechanism, the reaction of 3-(4-methoxyphenyl)but-3-en-2-one **485** with styrene oxide **491** was explored (Scheme 227). Disappointingly, no reaction was observed; even upon addition of benzoic acid to mimic the original reaction conditions. Notably, these studies were performed using a freshly prepared batch of starting material **485**.



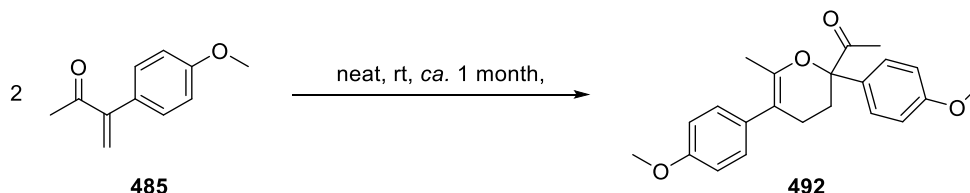
Scheme 227. Examining the reaction of 3-(4-methoxyphenyl)but-3-en-2-one (**485**) with styrene oxide (**491**).

Curiously, attempts to repeat the initial oxidation reaction using this fresh batch of starting material did not provide the same distribution of products, with a very different reaction profile observed by ¹H NMR analysis and negligible amounts of **487** formed. Despite the complexity of the ¹H NMR spectrum for the crude reaction mixture, it was possible to determine that, unlike in previous reactions, considerable amounts of the starting material remained. Furthermore, from the distinctive doublets at 3.26 and 3.05 ppm, with a coupling constant of 5.5 Hz, epoxide **488** was identified as being formed under the oxidative reaction conditions (Scheme 228).⁴⁷⁸ Based on the existence of both of these species together in significant quantities, in conjunction with the lack of reactivity observed between styrene oxide and the starting material, the mechanism presented in Scheme 225 was discounted.



Scheme 228. Formation of epoxy ketone **488** from the treatment of **485** with *m*CPBA.

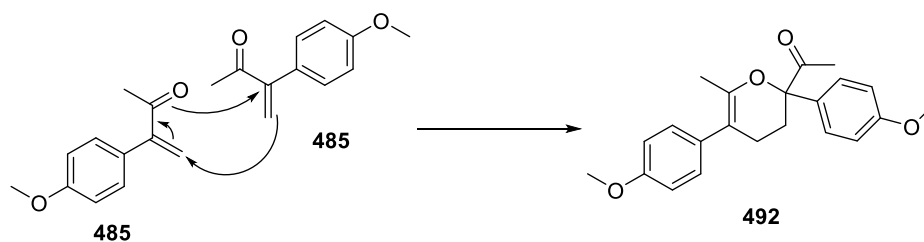
Based on the reproducibility issues, it was considered that the starting material may be degrading over time. Upon standing for a number of weeks, 3-(4-methoxyphenyl)but-3-en-2-one (**485**) was found to change from a colourless oil into a pale yellow solid. Analysis of the ^1H NMR spectrum for the crude solid indicated that the starting material had been completely consumed and the formation of predominantly one product was observed, which was purified and isolated by flash column chromatography. Spectroscopic analysis of the analytically pure material allowed for the structure to be elucidated. Most significantly, within the ^1H NMR spectrum the presence of two inequivalent sets of methyl and methoxy singlets in a 1:1 ratio as well as four distinct aromatic resonances of equal intensity implied that dimerisation had occurred to form an unsymmetrical species. Retention of a ketone functionality was determined by the characteristic downfield peak at 209.5 ppm within the ^{13}C NMR spectrum, which was further supported by the presence of a distinctive, strong absorption at 1712 cm^{-1} within the IR spectrum. These observations, in conjunction with a parent ion of m/z 375.1569 for the sodiated adduct, allowed for the unknown product to be identified as dihydropyran species **492** (Scheme 229).



Scheme 229. Dimerisation of **485** upon standing to afford substituted dihydropyran **492**.

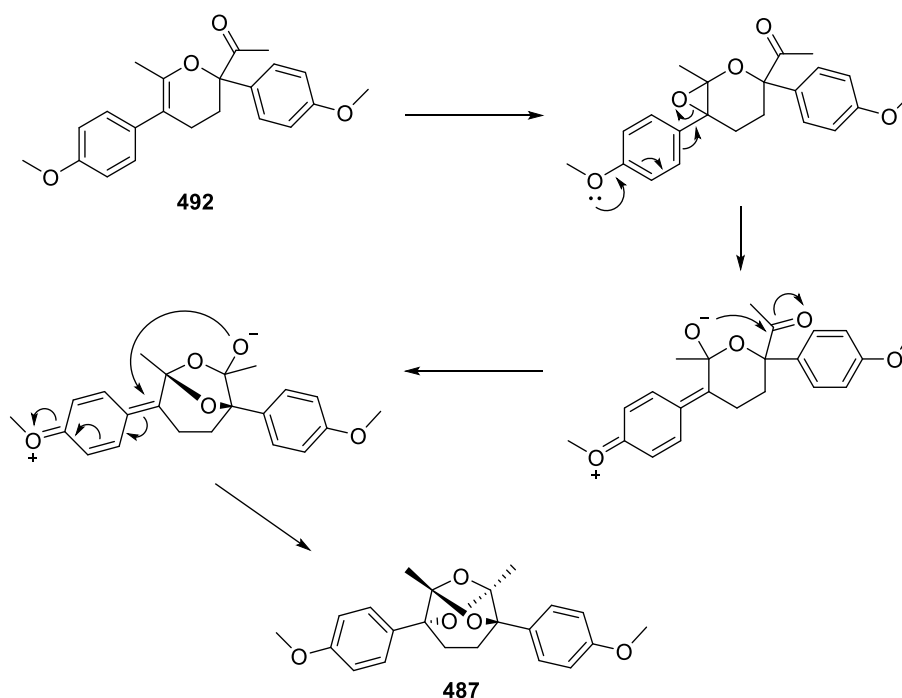
Left neat at room temperature, α -methylene ketone **485** spontaneously undergoes self-dimerisation presumably *via* a [4+2] cycloaddition reaction to form the novel and highly substituted dihydropyran **492** (Scheme 230).⁴⁷⁹⁻⁴⁸² Within this potentially inverse electron demand hetero Diels-Alder reaction, 3-(4-methoxyphenyl)but-3-en-2-one (**485**) functions as both the diene and dienophile, which has been reported previously for the dimerisation of other α -methylene ketones.^{479,480} The cyclisation proceeded relatively cleanly and in the absence of any catalyst or solvent, albeit relatively slowly. However, it is anticipated that the reaction time may be reduced with heating.⁴⁷⁹ To determine whether the acidic reaction conditions employed for the Baeyer-Villiger oxidation promote this cyclisation event, 3-(4-methoxyphenyl)but-3-en-2-one (**485**) was treated with 1.5 equivalents of benzoic acid in toluene for 2 hours. Negligible, if any,

dimerization was observed, suggesting that the material used for initial studies had cyclised prior to the developed reaction conditions being applied. Excitingly, the heterocyclic motif of **492** and its saturated congener are prevalent within many natural products and biologically active compounds.⁴⁸²⁻⁴⁸⁴ Structural modifications to reduce the electron density on the enone diene and/or employing a more electron rich dienophile may promote a more facile reaction; enabling access to a library of structurally diverse and interesting dihydropyran derivatives.⁴⁸⁰



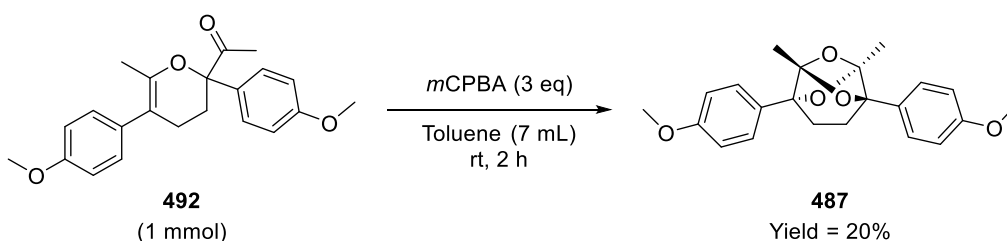
Scheme 230. Proposed mechanism for the dimerisation of 485 to 492.

Therefore, it is proposed that cage structure **487** was formed from **492** via a multi-step mechanism involving initial epoxidation of the dihydropyran ring by *m*CPBA (Scheme 231). Ring-opening of the epoxide, hemiketal formation and ring closure then generates the fused ring species **487**. This process is likely to be promoted by acid-catalysis and resonance stabilisation effects of the electron rich aromatic substituent. Again this is shown as a step-wise mechanism for clarity.



Scheme 231. Revised mechanism for the formation **487** from **485**.

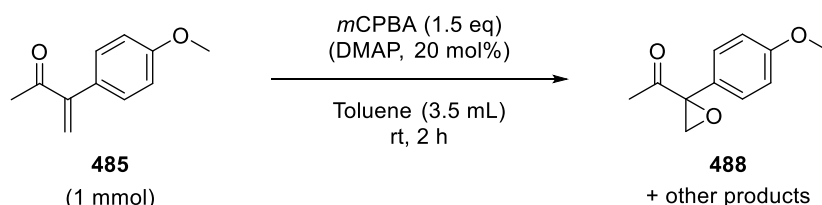
To test this hypothesis the developed oxidation conditions were applied to Diels-Alder adduct **492** and as anticipated **487** was formed, which was isolated in 20% yield as a white solid after purification by column chromatography (Scheme 232). Further optimisation is required to improve the selectivity and yield of this reaction, which may focus on the choice of oxidant, solvent and reaction temperature.



Scheme 232. Oxidation of dihydropyran **492** with *m*CPBA to afford **487**.

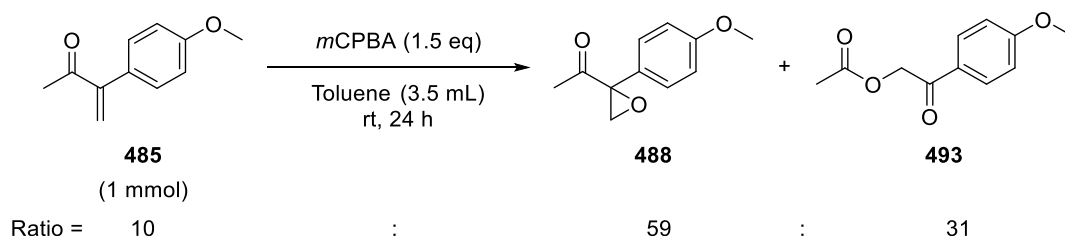
With a pure sample of α -methylene ketone **485** prepared, the focus was returned to the original aim of determining whether such substrates are amenable to the developed Baeyer-Villiger methodology. α -Methylene ketone **485** was treated with 1.5 equivalents of *m*CPBA for 2 hours both in the presence and absence of DMAP (20 mol%) (Scheme 233). Analysis of the crude reaction mixtures by ^1H NMR spectroscopy again indicated that several species were present, including epoxide **488**, which was formed in greater quantities when DMAP was omitted. Additionally, unrelated singlets at 4.82 ppm and 5.30 ppm were observed in both samples. Interestingly, the relative intensities of these signals was also dependent on the reaction conditions

employed. In contrast to the uncatalysed reaction, the singlet at 4.82 ppm was of higher intensity in the presence of DMAP, suggesting that the catalyst either promotes formation of the species attributed to this signal or inhibits formation of the compound associated with the singlet at 5.30 ppm.



Scheme 233. Attempted Baeyer-Villiger oxidation of 485 with *m*CPBA in the presence and absence of DMAP.

As considerable quantities of the starting material remained in both instances, the reactions were repeated for 24 hours. After this extended time period, the disparity in product selectivity became more pronounced and surprisingly higher consumption of the starting material was achieved within the uncatalysed system. With considerable quantities of both the proposed epoxide (**488**) and the unknown responsible for the peak at 5.30 ppm formed in this instance, attempts were made to isolate and identify these species. Following isolation by flash column chromatography, full characterisation of the analytically pure samples confirmed the structure of epoxy ketone **488**, which was isolated as a pale yellow oil, and also revealed that the singlet at 5.30 ppm could be attributed to the methylene protons of keto ester **493** (Scheme 234). This ester was isolated as a colourless solid, with all spectroscopic data consistent with literature values.⁴⁸⁵ Whilst small amounts of other species including the unknown at 4.82 ppm were present, **488** and **493** represented the primary reaction components in the absence of any catalyst. The ratio of starting material **485**: epoxide **488** : keto ester **493** was determined as 10:59:31 by analysis of the relative integrals for the characteristic peaks within the crude ¹H NMR spectrum.

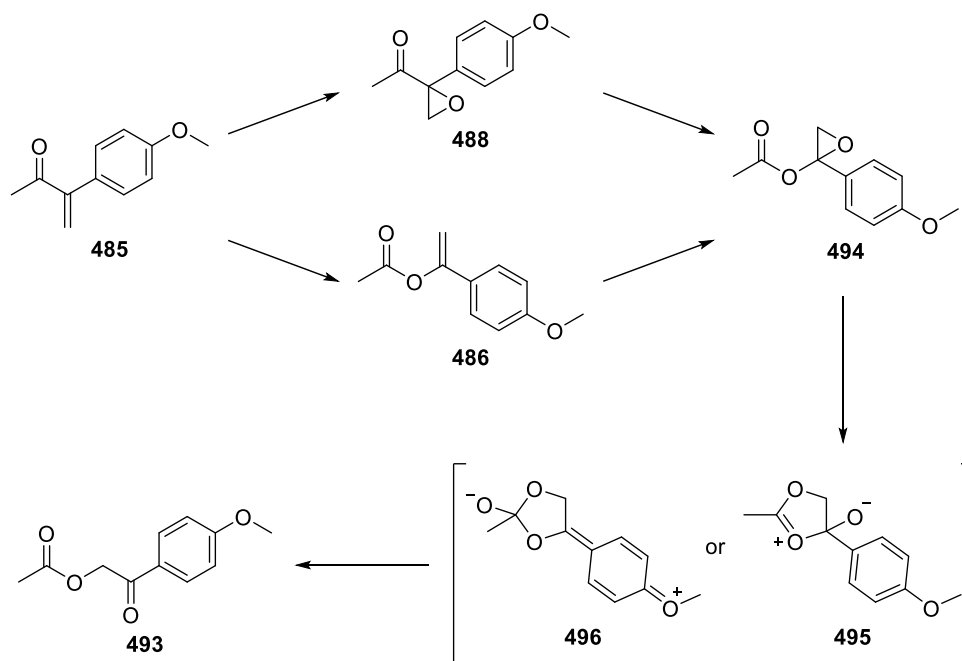


Scheme 234. Ratio of reaction products for the oxidation of 485 with 1.5 equivalents of *m*CPBA.

For the analogous oxidation of α,β -ketones containing an internal double bond, epoxidation of the starting material was not competitive with the desired Baeyer-Villiger oxidation and only negligible quantities of the corresponding epoxy ketones were ever observed. The increased favourability of epoxidation for **485** can be rationalised by the enhanced nucleophilicity of the

double bond in this instance; arising from donation of electron density from the methoxy group into the π -orbitals of the alkene *via* resonance.

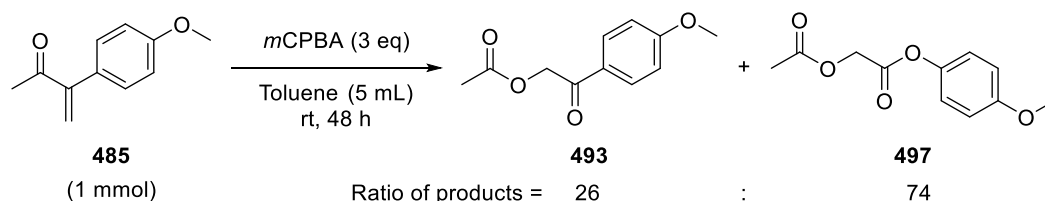
It is proposed that keto ester **493** is formed *via* the same mechanism as α -acetoxy aldehyde **341** (Scheme 235). Initially, epoxy ester **494** is generated from a consecutive Baeyer-Villiger oxidation and epoxidation of **485** with 2 equivalents of *m*CPBA. Intramolecular cyclisation and rearrangement *via* either cyclic species **495** or **496** then affords the observed keto ester product **493**. Formation of this by-product also helps substantiate the mechanism provided for the formation of **341**. However, for the formation of **493** the order of the initial 2 oxidation steps to form epoxy ester **494** remains unclear. Due to the more facile epoxidation of **485** relative to other substrates examined, it is conceivable that epoxy ketone **488** may be generated initially and then undergo subsequent Baeyer-Villiger oxidation to provide intermediate **494**. Alternatively, if the rate of Baeyer-Villiger oxidation is higher, the normal sequence of transformations may be followed; initially affording ester **486**. Epoxidation of the ester (**486**), which contains a more reactive double bond than the ketone starting material, may then rapidly ensue. Both scenarios may lend explanation to the absence of any appreciable amount of the desired ester product **486** and for the latter epoxidation of **485** would represent a competitive process, with the epoxy ketone **488** existing as a spectator only. It is feasible that either one or both pathways may be in operation.



Scheme 235. Proposed mechanism for the formation of ester **493** from **485**.

In an attempt to improve the selectivity for keto ester **493**, the reaction was repeated in the presence of 3.0 equivalents of *m*CPBA for 48 hours. From analysis of the ^1H NMR spectrum for the crude reaction mixture it was determined that complete consumption of the starting material

had been achieved and of particular significance no epoxide (**488**) was observed. This finding is extremely interesting as it suggests that epoxide **488** may undergo Baeyer-Villiger oxidation with *m*CPBA. Although it remains unclear whether or not this is the major pathway for the formation of epoxy ester **494**, the Baeyer-Villiger oxidation of an epoxy ketone to form the corresponding epoxy ester is less commonly reported.^{348,363,486} The reaction mixture was instead found to comprise primarily of keto ester **493** and novel diester **497** in a 26:74 ratio (Scheme 236). In support of this proposed structure, the two IR absorbances at 1776 and 1749 cm⁻¹ (*cf.* keto ester 1746, 1691 cm⁻¹) as well as the two resonances within the ¹³C NMR spectra at 170.5 and 166.9 ppm (*cf.* keto ester 190.7, 170.7 ppm) are characteristic of two distinct ester moieties. Additionally, the upfield shift of the methylene protons is indicative of oxygen insertion adjacent to the aromatic substituent rather than the methylene unit. It is these methylene protons of diester **497** that are responsible for the singlet observed at 4.82 ppm within all ¹H NMR spectra and was previously found to be the major product in the DMAP promoted reaction performed for 24 hours.



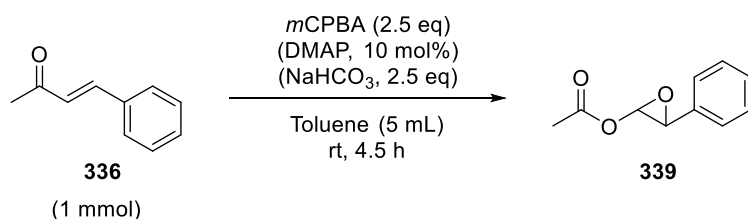
Scheme 236. Ratio of reaction products from the oxidation of **485** with 3 equivalents of *m*CPBA.

Diester **497** is thought to form *via* the Baeyer-Villiger oxidation of the ketone moiety of keto ester **493**. This result was not entirely unexpected as oxidation of a ketone involving migration of a *p*-methoxyphenyl group was found to be particularly facile during the study of substituted acetophenones and over-oxidation is commonly observed within peracid oxidations, as encountered within the formation of formate ester **354**. The higher quantities of diester (**497**) relative to monoester (**493**) observed in the DMAP catalysed system, is consistent with this latter Baeyer-Villiger oxidation proceeding with rate-determining addition in the absence of a catalyst, as described previously for *p*-methoxyacetophenone. It may be anticipated that employing an excess of the *m*CPBA reagent will provide a high yielding procedure for the synthesis of this novel, oxygen rich species from α-methylene ketone **485**. Unfortunately, whilst DMAP enhances the rate of oxidation of intermediate keto ester **493** it appears to retard its rate of formation.

2.3.10 Optimisation for by-product formation

2.3.10.1 Formation of epoxy ester

Attention was then focussed on optimising the reaction conditions for the formation of the over-oxidation by-products derived from (*E*)-4-phenyl-3-buten-2-one (**336**), namely epoxy ester **339**, α -acetoxy aldehyde **341** and formate ester **354**, as these species are interesting in their own right. Initially, selective formation of epoxy ester **339** was targeted. It was hypothesized that the acid-catalysed intramolecular cyclisation and rearrangement of epoxy ester **339**, which leads to its degradation, may be prevented by performing the reaction in the presence of a base. Pleasingly, employing 2.5 equivalents of sodium bicarbonate as an additive improved the selectivity for epoxy ester **339** (Table 29, entries 1 and 2). As anticipated, it was deduced that the base limits undesired rearrangement to aldehyde **341** rather than promoting epoxidation itself. This result also helps corroborate the acid promoted mechanism proposed for aldehyde formation. However, the sodium bicarbonate appears to slightly retard epoxidation of vinyl ester **337**, which is consistent with literature reports that epoxidations performed with peracids may be acid catalysed.⁴⁸⁷ Unexpectedly, similar selectivity for epoxy ester **339** was achieved using 10 mol% DMAP as the additive (Table 29, entry 3). Whilst this catalyst has been observed to inhibit *m*CPBA promoted epoxidation of vinyl ester **337**, it also appears to prevent degradation of epoxy ester **339** to some extent, particularly at a higher concentration of *m*CPBA (2.5 equiv.); limiting the formation of aldehyde **341** and its oxidised derivatives. It is thought that this observation may be attributable to the weakly basic nature of the catalyst or degradation of the peracid in its presence. Interestingly, performing the reaction in the presence of both additives gave superior results, with 46% selectivity for epoxy ester **339** achieved and only very small amounts of degradation were observed (Table 29, entry 4). Unfortunately, extending the reaction time to 24 hours under these conditions did not promote further conversion of the vinyl ester **337** but instead increased the potential for degradation, with greater amounts of aldehyde **341** observed. In a further attempt to promote epoxidation of the vinyl ester **337**, higher concentrations of *m*CPBA were employed in the presence of both additives. However, whilst consuming higher levels of the vinyl ester, this resulted in a considerable amount of over-oxidation. Nevertheless, the selectivity achieved using the conditions outlined in entry 4 (Table 29) was a pleasing result for a 2 step, one-pot synthesis of epoxy ester **339**. Attempts were not made to isolate this species, as it is relatively unstable.

Table 29. Attempts to improve the selectivity of the *m*CPBA oxidation for epoxy ester **339**.

Entry	Additive	Ket. 336	Ester 337	Epox. 339	Ald. 341	Acid 353	Form. 354	Epox. 338
1	-	6	12	4	30	14	29	5
2	NaHCO ₃	-	43	31	18	2	3	3
3	DMAP	-	26	30	25	13	4	2
4	NaHCO ₃ , DMAP	-	47	46	2	2	1	2

Product ratios were determined by ¹H NMR spectroscopic analysis.

It is anticipated that treatment of isolated vinyl ester **337** with only a slight excess of *m*CPBA in the presence of sodium bicarbonate and DMAP may provide a more effective route for the synthesis of epoxy ester **339**. The smaller excess of *m*CPBA should limit the potential for over-oxidation. Often the Baeyer-Villiger oxidation and epoxidation reactions are favoured under different reaction conditions. Thus, by accessing epoxy ester **339** *via* a 2 step protocol involving isolation of the vinyl ester **337**, rather than a one pot synthesis, will allow for the conditions to be optimised for the epoxidation step, particularly with regards to the peracid and solvent used. However, this investigation was beyond the scope of this work.

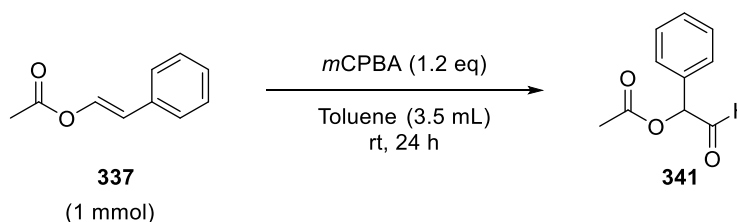
2.3.10.2 Synthesis of α -acetoxy aldehyde

Selective synthesis of aldehyde **341** was particularly challenging, as this species is formed *via* two consecutive oxidation processes but is degraded by a third, with oxidation to the corresponding carboxylic acid or formate ester being particularly facile (*cf.* Table 29, entry 1). Thus, it was imperative to limit the amount of oxidant as far as possible, whilst employing sufficient quantities to promote the desired oxidations. Crucially, all reaction conditions explored excluded DMAP and sodium bicarbonate, as from previous studies these additives were found to inhibit formation of the aldehyde (Table 29). Unfortunately, even employing these strategies, poor selectivity for the aldehyde was observed (<40%), despite numerous variations within the reaction parameters. At higher quantities of *m*CPBA or extended reaction times over-oxidation to **353** and **354** was commonly observed (2.5 equiv., 24 hours), whilst at lower levels of *m*CPBA or shorter

reaction times a large number of reaction products were formed, with very little selectivity. Additionally, in some instances inconsistent results were obtained with regards to the relative ratio of epoxy ester **339** : aldehyde **341**. Curiously, multiple attempts at performing the reaction under identical conditions sometimes saw opposite selectivity between these two species; with large amounts of epoxy ester relative to the aldehyde sometimes being observed and in other instances negligible amounts. As the rearrangement is acid catalysed, this observation may be rationalised by differing concentrations of *m*CPBA in solution. This may have been an artefact of the batch of *m*CPBA employed or the timing of *m*CPBA precipitation from solution.

Consequently, attempts were made to optimise the formation of aldehyde **341** from vinyl ester **337** instead, as it was thought this would allow better control over the level of oxidation. It was determined that performing the oxidation of vinyl ester **337** with a small excess (1.2 equiv.) of *m*CPBA for 24 hours gave the best selectivity for aldehyde **341** (42%, Table 30).

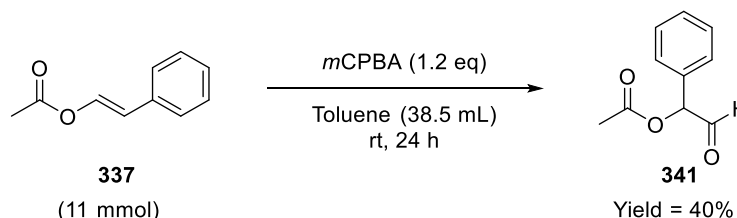
Table 30. Optimisation of reaction conditions for the formation of aldehyde 341.



Entry	Ester 337	Epox. 339	Ald. 341	Acid 353	Form. 354	Epox. 338
1	16	25	42	-	17	-

Product ratios were determined by ^1H NMR spectroscopic analysis.

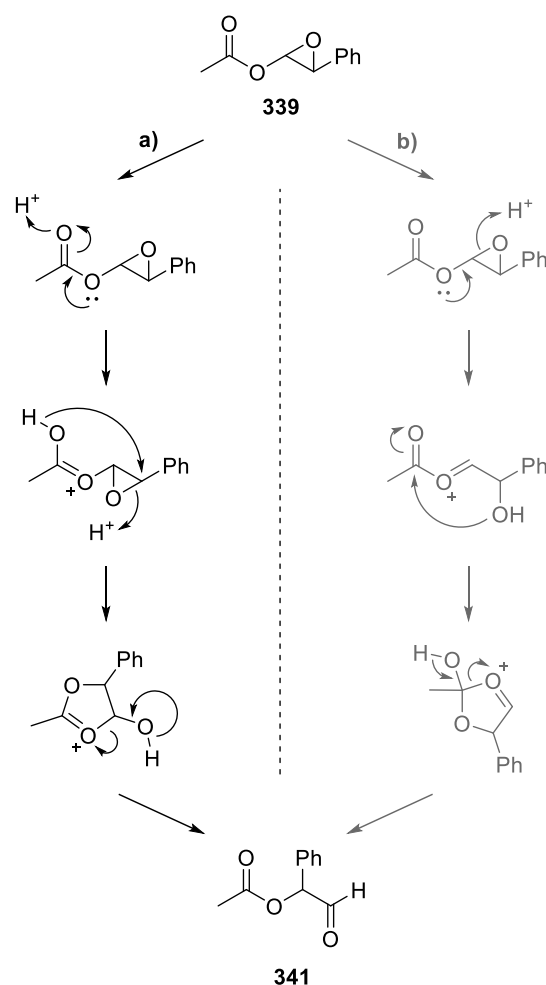
Upon scale up of the reaction, aldehyde **341** was successfully isolated in 40% yield (Scheme 237). This is a particularly pleasing result as this species is known to be particularly unstable and is often reduced *in situ* to the corresponding 1,2-diol.



Scheme 237. Optimised conditions for the synthesis of aldehyde 341 from vinyl ester 337.

As previously detailed, it is proposed that aldehyde **341** is formed *via* the acid catalysed cyclisation and rearrangement of epoxy ester **339** (Scheme 238, pathway a or b). In support of

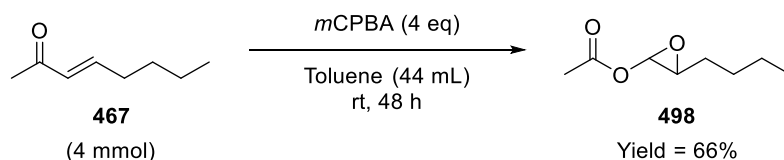
this transformation, epoxide **339**, observed within samples of the crude reaction mixture, was found to degrade to aldehyde **341** over a 24 hour period. However, it was not possible to isolate and subject epoxide **339** to the reaction conditions to confirm such a hypothesis. Whilst the identity of the substituent at the β -position of the alkene would not be expected to greatly influence pathway b, the opposite is true for pathway a as bond making and breaking occurs at this position and a positive charge may be forming. Substituents that are less able to stabilise the positive charge, either due to inductive or resonance effects, would be expected to retard a reaction proceeding *via* pathway a but not pathway b.



Scheme 238. Mechanistic proposal for the formation of aldehyde **341.**

Therefore, it was considered that by performing the oxidation of (*E*)-3-octen-2-one **467** with excess *m*CPBA (4 equiv.) it may allow for the two pathways to be distinguished, as the *n*-butyl group is poorly electron releasing (Scheme 239). The reaction was conducted in the absence of a catalyst as previous studies had demonstrated that, due to the poor migrating group, the oxidation of (*E*)-3-octen-2-one **467** did not proceed with rate-determining addition and was not catalysed. Significantly, no rearrangement was observed and epoxyster **498** was afforded exclusively, as

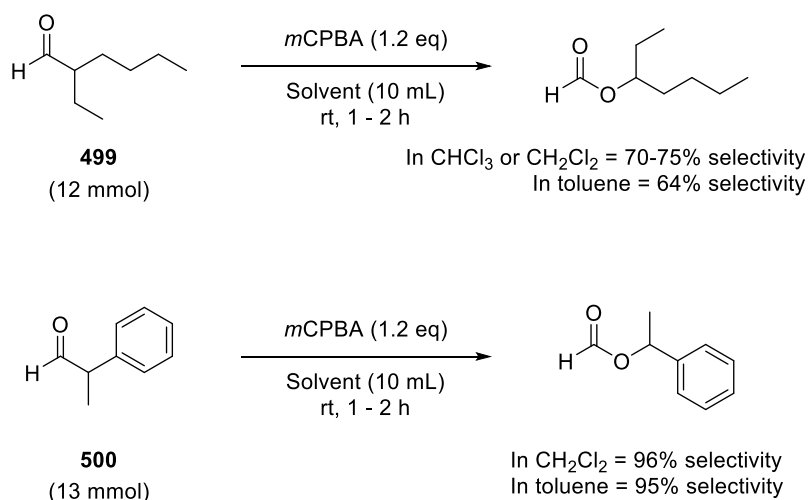
determined by ^1H NMR analysis of the crude reaction mixture. 3-Butyloxiran-2-yl acetate **498** was subsequently isolated in 66% yield following purification by column chromatography. This helps to substantiate the proposal that aldehyde **341** is derived from epoxy ester **339** and implies that it is formed *via* pathway a (Scheme 238). Additionally, this represents a novel method for the synthesis of epoxy ester **498** directly from the corresponding α,β -unsaturated ketone **467**. Similar oxidations have been reported within the literature using *m*CPBA but this method appears to be more commonly applied to cyclic substrates.^{488,489}



Scheme 239. Application of the uncatalysed oxidation conditions to the synthesis of epoxy ester **498** from (*E*)-3-octen-2-one (**467**).

2.3.10.3 Synthesis of formate ester

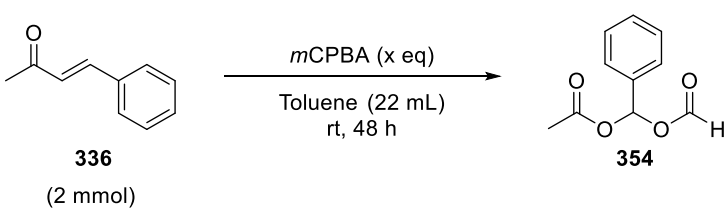
Finally, reaction conditions for the selective synthesis of formate ester **354** were developed. As both sodium bicarbonate and DMAP have been found to hinder the formation of aldehyde **341**, which is a precursor to formate ester **354**, the reaction was explored in the absence of such additives. The Baeyer-Villiger oxidation of aldehydes has previously been reported to favour formation of the formate ester over the carboxylic acid in the presence of peracid oxidants, such as *m*CPBA, and for reactions run in aprotic solvents such as dichloromethane, chloroform and toluene.⁴⁰⁹ For instance, Lehtinen *et al.* found that the *m*CPBA oxidation of 2-ethylhexanal (**499**) afforded the formate ester in ~70-75% selectivity in the chlorinated solvents and ~64% selectivity in toluene (Scheme 240).⁴⁰⁹ Interestingly, the authors also highlighted that substrates containing a phenyl group α to the carbonyl, as is the case for aldehyde **341**, had a greater propensity for alkyl migration over hydrogen migration resulting in generation of the corresponding formate ester.⁴⁰⁹ In this context, 2-phenylpropionaldehyde (**500**) was reported to preferentially oxidise almost entirely to the formate ester for reactions conducted in either dichloromethane or toluene (96% and 95% respectively).⁴⁰⁹ Conversely, polar protic alcohol based solvents promoted the formation of large quantities of the carboxylic acid.⁴⁰⁹



Scheme 240. Selectivities reported for the formation of the formate ester over the carboxylic acid in the *m*CPBA oxidation of **499** and **500**.⁴⁰⁹

On the basis of this, it was anticipated that the previously devised reaction conditions (*m*CPBA, toluene) would promote selective formation of formate ester **354** but the reaction required more forcing conditions to proceed to completion. Although marginally better selectivity was reported in the literature example using dichloromethane, this was not explored as a potential solvent due to the associated regulatory restrictions.^{409,428} In order to improve the extent of the oxidation towards **354**, the reaction time and amount of oxidant were increased (Table 31, *cf.* Table 29, entry 1, 29% selectivity). Employing 3 equivalents of *m*CPBA, the minimum required to account for each of the oxidation steps, only 66% selectivity for the formate ester was achieved, even after an extended reaction time of 48 hours (Table 31, entry 1). Pleasingly, complete consumption of starting material **336** was observed after 48 hours in the presence of four equivalents of *m*CPBA and excellent selectivity for formate ester **354** (96%) was attained (Table 31, entry 2). Interestingly, the only by-product observed under the latter conditions was small amounts of epoxy ketone **338**, further confirming that Baeyer-Villiger oxidation of this species is unfavourable.

Table 31. Developing reaction conditions for the selective formation of formate ester **354.**



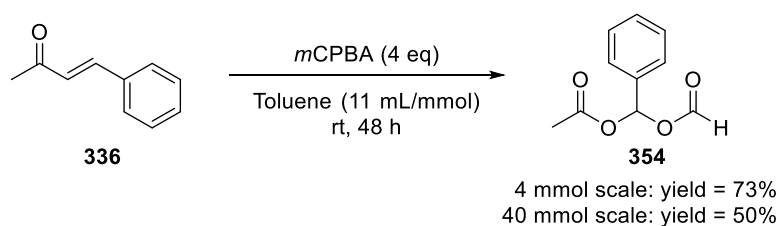
336
(2 mmol)

354

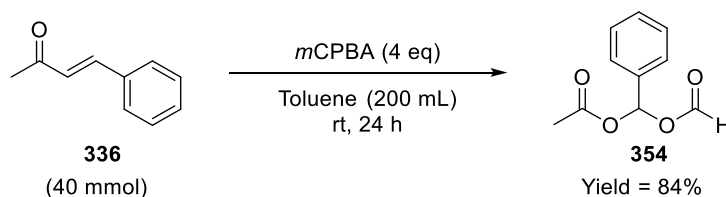
Entry	<i>m</i> CPBA (equiv.)	Ket. 336	Ester 337	Epox. 339	Ald. 341	Acid 353	Form. 354	Epox. 338
1	3.0	1	3	2	22	-	66	6
2	4.0	-	-	-	-	-	96	4

Product ratios were determined by ¹H NMR spectroscopic analysis.

Thus, α,β -unsaturated ketone **336** was vigorously stirred with 4 equivalents of *m*CPBA in toluene for 48 hours, after which the reaction mixture was washed with saturated aqueous sodium bicarbonate solution. Purification of the crude residue by flash column chromatography afforded (formyloxy)(phenyl)methyl acetate (**354**) as a colourless oil in 73% yield (Scheme 241). The slight discrepancy observed between conversion and isolated yield is most likely attributable to hydrolysis of the formate ester upon aqueous work-up or acid-catalysed degradation on the silica gel during purification. Alternatively, the slightly lower than expected yield may be a result of the large number of washes required to dissolve and remove the *m*CBA precipitate. These additional washes may have also inadvertently extracted any carboxylic acid by-product (**353**) into the aqueous washings, consequently distorting the conversion obtained. With the optimised conditions established, the reaction was successfully scaled-up to 40 mmol with respect to (*E*)-4-phenyl-3-buten-2-one (**336**), with a 50% isolated yield obtained.

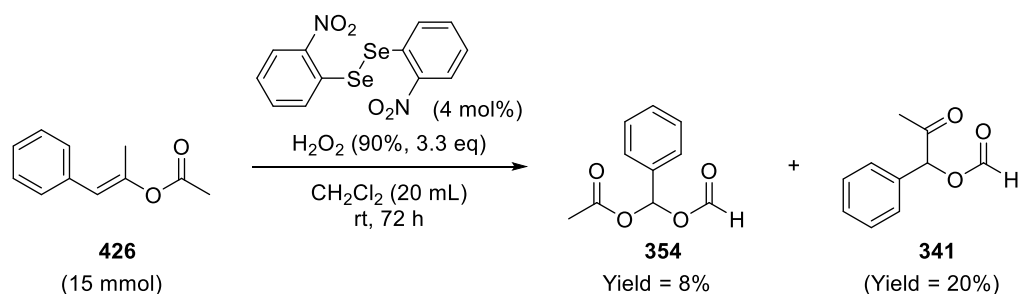

Scheme 241. Synthesis of formate ester **354 from (*E*)-4-phenyl-3-buten-2-one (**336**).**

Subsequent work within the group has determined that comparable conversion can be achieved in a reduced time of 24 hours when the reaction is performed at double the concentration (Scheme 242). Additionally, on a 40 mmol scale the formate ester **354** was afforded cleanly in 84% isolated yield by performing multiple sodium carbonate washes; avoiding the need for silica gel column chromatography.



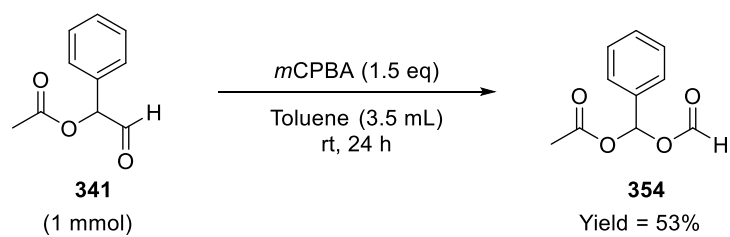
Scheme 242. Revised method for the synthesis of formate ester **354** from (*E*)-4-phenyl-3-buten-2-one (**336**).

Therefore, a high yielding and efficient method for the direct synthesis of highly oxygen rich species **354** has been developed, with the optimised conditions highlighted in Scheme 242. This reaction is operationally simple with only basic purification necessary and does not require the exclusion of air. To the best of our knowledge only one literature report exists for the synthesis of **354**, which was published in 1987 by Syper.⁴¹³ Oxidation of vinyl ester **426** using bis(2-nitrophenyl) diselenide activated 90% H_2O_2 for 72 hours was reported to afford formate ester **354** in a very poor yield of 8% (Scheme 243).⁴¹³ Therefore, the developed methodology represents a considerable improvement.



Scheme 243. Existing method for the preparation of formate ester **354** reported by Syper.⁴¹³

It is proposed that formate ester **354** is formed from the Baeyer-Villiger oxidation of aldehyde **341**. To substantiate this hypothesis, the developed oxidative reaction conditions were applied to an isolated sample of aldehyde **341** (Scheme 244). As anticipated, treatment of aldehyde **341** with 1.5 equivalents of *m*CPBA resulted in quantitative conversion to formate ester **354** after 24 hours, which was isolated in 53% yield after work-up and purification by column chromatography. Experimentally, the multi-step reaction pathway for the formation of formate ester **354** from (*E*)-4-phenyl-3-buten-2-one (**336**) has been fully characterised, with many of the intermediates successfully isolated. Whilst the selective syntheses of the regioisomeric carboxylic acid **353** has not yet been explored, it may be envisaged that variation of the oxidant and solvent would make this permissible, with O_2 in an alcoholic solvent identified as potentially suitable conditions based on literature reports.⁴⁰⁹



Scheme 244. Oxidation of aldehyde **341** with *m*CPBA to afford formate ester **354**.

2.4 Conclusion

N-Oxides have been found to successfully promote Baeyer-Villiger oxidations performed with *m*CPBA. The developed methodology benefits from short reaction times, requires only a small excess of oxidant and may be performed at room temperature without the need for dry or inert conditions. Comparable results were achieved when using preformed DMAPO or when generating the catalytic active species *in situ* from readily available DMAP. When employing this amine as the precatalyst, it is proposed that either the corresponding *N*-oxide is generated under the oxidative reaction conditions, which may function as a co-catalyst with the *m*CBA, or that a quaternary ammonium carboxylate salt is formed, which may act as a bifunctional catalyst. Irrespective of its identity, the catalytic species is thought to function as a hydrogen bond acceptor to facilitate concerted proton transfer within the addition step. Thus, the small portfolio of reactions employing *N*-oxides as novel hydrogen bond catalysts has been successfully extended. It was hypothesized that the devised catalytic system enhances the rate of any Baeyer-Villiger oxidation proceeding with rate-determining addition and thus provided a tool to examine the rate-determining step for each substrate under the developed reaction conditions. Such a phenomenon has not been previously reported and the rate limiting step has typically remained elusive for the majority of published oxidations. A catalytic effect was also observed in the presence of sodium carboxylates; indicating that they may also function as general bases within the Baeyer-Villiger oxidation. To date, a general base catalysed addition step has not been postulated for the Baeyer-Villiger oxidation of ketones.

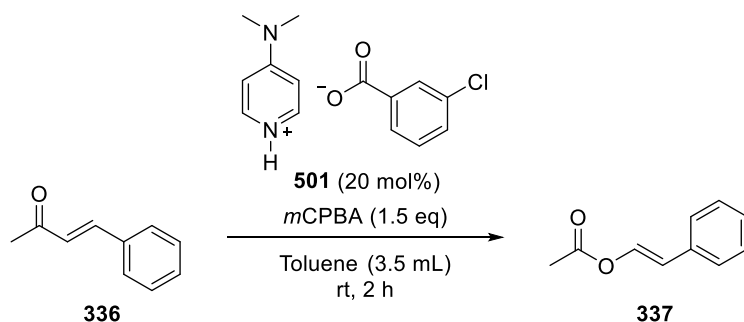
As well as increasing the rate of the desired oxidation, the application of DMAP was found to retard the rate of epoxidation reactions. Thus, a highly chemo- and diastereoselective method for the preparation of vinyl esters *via* the oxidation of α,β -unsaturated ketones has been developed. The devised oxidation protocol was found to be amenable to a broad range of substrate classes, with excellent functional group tolerance; affording the corresponding vinyl esters, including a number of novel species, in moderate to good yields. Preferential vinyl group migration was observed in all instances, demonstrating that the migratory aptitude of a styryl group is superior to a tertiary alkyl group under the developed conditions. In some instances, the selectivity of the oxidation for the vinyl ester could be improved in the presence of DMAP, despite a catalytic effect not being observed. The uncatalysed variant of the oxidation protocol was successfully applied within the two step synthesis of unsymmetrical α -diketone **435** and related α,α -dialkoxy ketone **434** from commercially available starting material; thereby reducing the number of synthetic steps by more than half compared to current approaches. This methodology was also successfully extended to saturated ketones.

A series of over oxidation by-products generated from the reaction of (*E*)-4-phenyl-3-buten-2-one (**336**) with *m*CPBA were isolated and fully characterised, with the entire sequence of transformations elucidated. Reaction conditions were optimised for the preparation of these high oxidation state species, with particular success achieved in establishing a high yielding, operationally simple protocol for the synthesis of formate ester **354**.

The reactions of 3-(4-methoxyphenyl)but-3-en-2-one **485** were explored. Upon standing neat, this electron rich α -methylene ketone was found to spontaneously undergo self-dimerisation to generate novel, highly substituted dihydropyran **492**. Oxidation of this cyclic species with *m*CPBA provided access to novel oxygen rich cage compound **487**. Alternatively, oxidation of 3-(4-methoxyphenyl)but-3-en-2-one (**485**) with *m*CPBA afforded novel diester **497**; for which the Baeyer-Villiger oxidation of an epoxy ester was observed.

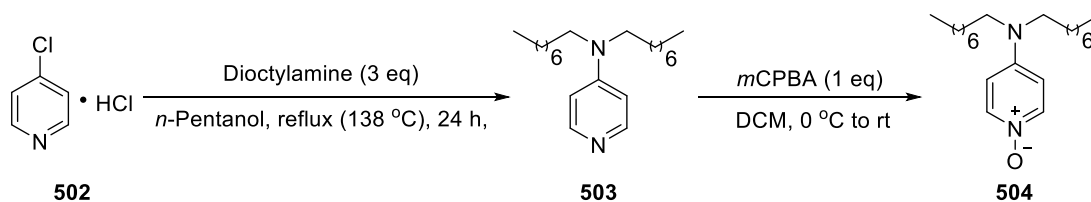
2.5 Future work

Subsequent studies may focus on probing the reaction mechanism further. To elucidate information on the catalytically active species within the DMAP promoted Baeyer-Villiger oxidation, quaternary ammonium salt **501** may be prepared and applied to the optimised reaction conditions (Scheme 245). It may be possible to distinguish between the reaction rates for the oxidation performed in the presence of this salt and preformed DMAPO; allowing for the catalytically active species in the DMAP system to be identified. Additionally, to examine the role of the carboxylic acid by-product, the reaction may be repeated using purified *m*CPBA. A reduction in reaction progress would indicate that the carboxylic acid is participating as a co-catalyst. Whilst this reaction was not conducive to kinetic studies due to the appreciable background rate, formation of side products and loss of homogeneity, it is hoped that a computational study may elucidate further information.



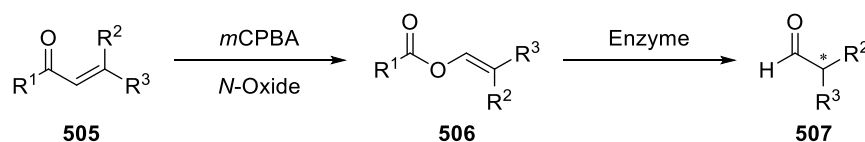
Scheme 245. Application of pre-formed quaternary ammonium salt **501** to the Baeyer-Villiger oxidation of (*E*)-4-phenyl-3-buten-2-one with *m*CPBA.

Improving the solubility of the *N*-oxide catalyst constitutes a further area for potential development. Due to the non-polar nature of the solvents employed, the concentration of catalytically active *N*-oxide within the organic reaction media may be low. Therefore, it is of particular interest to explore the potential of more ‘fatty’ *N,N*-dialkyl based derivatives of DMAP(O), such as **503**(**504**), to catalyse the reaction.⁴⁹⁰ As shown in Scheme 246, **504** may be easily synthesized in 2 steps from the HCl salt of 4-chloropyridine (**502**). The first of these involves nucleophilic aromatic substitution (S_NAr) of 4-chloropyridine with dioctylamine to generate **503** and the second step would involve oxidation of amine **503** to the desired *N*-oxide **504** using *m*CPBA.^{6,491} Alternatively, a solid supported catalyst could be developed.



Scheme 246. Synthesis of long chain amine *N*-oxide **504**.^{6,491}

Trisubstituted vinyl acetates, bearing a substituent on the β -carbon of the olefin moiety (**506**), have been identified as particularly valuable synthetic intermediates. Specifically, trisubstituted vinyl acetates may undergo enantioselective hydrolysis by a lipase or esterase enzyme to afford chiral aldehydes **507** (Scheme 247).⁴⁹² Thus, future work will focus on extending the substrate scope to trisubstituted α,β -unsaturated ketones with this substitution pattern (**505**). Additionally, owing to the relatively selective oxidation of *trans*-cinnamaldehyde to the corresponding vinyl formate, it is hoped that a range of formate esters may also be prepared from the corresponding aldehydes using the developed methodology.

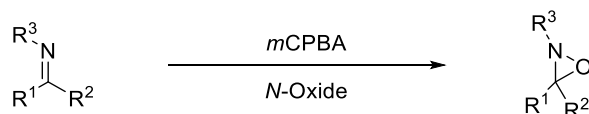


Scheme 247. Application of the developed methodology for the preparation of trisubstituted vinyl acetates, which may undergo enantioselective hydrolysis to afford chiral aldehydes.⁴⁹²

Nucleophilic addition constitutes the rate-determining step for many of the peracid oxidations examined. If, as proposed, the *N*-oxide catalyses these reactions by functioning as a hydrogen bond catalyst to aid concerted proton transfer from the nucleophile, it is conceivable that this class of organocatalyst may also improve the efficiency of other related nucleophilic addition reactions. Such reactions would need to fulfil similar criteria to ensure addition of the nucleophile is rate determining and involves concerted proton transfer, which include: a carbonyl compound that is poorly electrophilic (electron rich, sterically congested carbonyl), a poor nucleophile (electron poor, sterically encumbered), a poorly ionising solvent and a rapid second step.³²¹

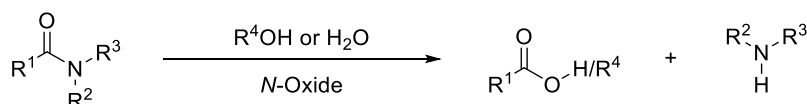
Thus, the peracid oxidation of imines to form oxaziridines was immediately identified as a logical extension for examining the generality of *N*-oxides within this role (Scheme 248). Whilst there was initially some controversy surrounding the mechanism for oxaziridine formation, with both an epoxidation and Baeyer-Villiger type pathway considered, it is generally accepted that the oxidation entails two steps (Baeyer-Villiger type mechanism).⁴⁹³⁻⁴⁹⁵ Reminiscent of the Baeyer-Villiger oxidation, it has been suggested that in some instances addition to the C=N bond of the

imine is rate determining and the reaction may be catalysed by carboxylic acids.⁴⁹³⁻⁴⁹⁵ This reactivity is unsurprising as imines are less electrophilic than ketones.



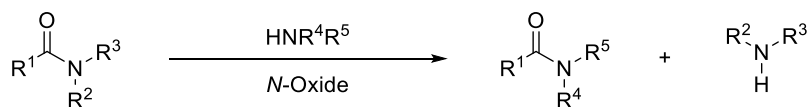
Scheme 248. Application of *N*-oxides as hydrogen bond catalysts within the peracid oxidation of imines to form oxaziridines.

Additionally, the alcoholysis/hydrolysis of amides may be amenable to catalysis by *N*-oxides (Scheme 249). Typically, amides are highly stable carbonyl compounds due to donation of electron density from the nitrogen to the carbonyl *via* conjugation of the nitrogen lone pair. Tuning the substituents of the oxygen based nucleophiles will allow for their reactivity to be adjusted accordingly with the aim of promoting a facile reaction that entails rate determining addition.



Scheme 249. Application of *N*-oxides as hydrogen bond catalysts within the alcoholysis/hydrolysis of amides.

Based on the success of alkyl ammonium salts in catalysing the addition step of transamidation and ring-opening polymerisation reactions *via* hydrogen bonding interactions,^{435,442-446,469} it was considered that these transformations may also be susceptible to catalysis by *N*-oxides (Scheme 250).

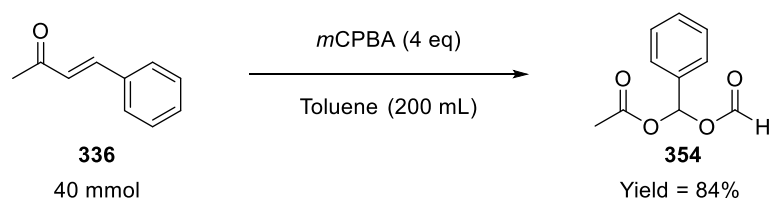


Scheme 250. Application of *N*-oxides as hydrogen bond catalysts within transamidations.

3 Investigating (formyloxy)(phenyl)methyl acetate as a novel formylating reagent

3.1 Introduction

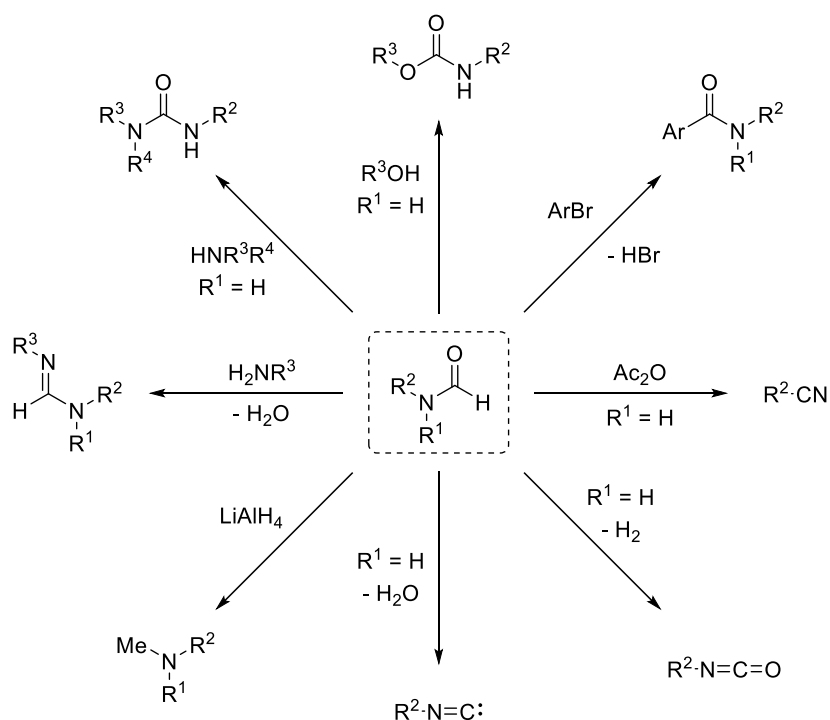
As described in Chapter 2, a high yielding and operationally simple protocol has been developed for the one step synthesis of formate ester **354** in high purity from commercially available and inexpensive α,β -unsaturated ketone **336** (Scheme 251). Since this methodology was found to be readily scalable and does not require complicated purification procedures, we were interested in ascertaining the synthetic applications of **354**. Specifically, the potential for this formate ester (**354**) to function as a novel, relatively bench stable formylating reagent was examined.



Scheme 251. Method for the synthesis of formate ester **354** from (*E*)-4-phenyl-3-buten-2-one (**336**).

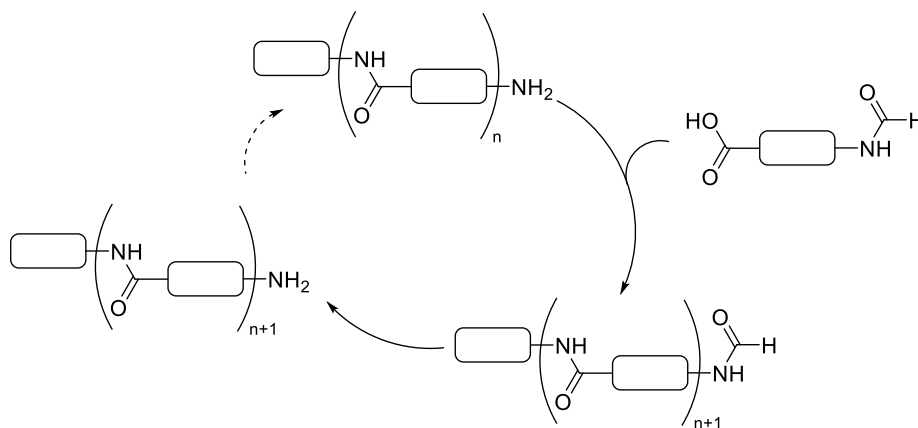
3.1.1 Applications of formamides

N-Formylation is a transformation of fundamental importance in synthetic organic chemistry, as it provides access to the highly versatile formamide functional group.^{496,497} Highlighting its synthetic utility, *N*-formyl derivatives have been applied as precursors to formamidines,⁴⁹⁸ ureas,⁴⁹⁹ carbamates,⁴⁹⁹ aryl amides,⁵⁰⁰ *N*-methylarylamines,⁵⁰¹ isocyanates,⁵⁰² nitriles⁵⁰³ and in particular isocyanides,^{504,505} which may be employed within multicomponent reactions such as the Passerini and Ugi reactions (Scheme 252).^{506,507} Additionally, dimethylformamide (DMF) is commonly employed not only as a polar solvent but also as a reagent in the Vilsmeier-Haack reaction.^{508,509} Due to their ability to undergo such varied functional group transformations, formamides have consequently found much use as intermediates in the synthesis of pharmaceuticals,⁵¹⁰⁻⁵¹² fungicides and herbicides.⁵¹³



Scheme 252. Functional group transformations of formamides.

Alternatively, the formyl group may be installed temporarily as a protecting group, with selective removal possible under mild conditions.⁵¹⁴⁻⁵¹⁶ This strategy is of particular relevance within peptide synthesis, which utilises *N*-formyl amino acid derivatives to prevent undesired polymerisation and side chain reaction (Scheme 253).⁵¹⁷⁻⁵²⁰



Scheme 253. Application of an *N*-formyl protecting group within peptide synthesis.⁵²¹

As well as finding diverse applications within organic synthesis, formamides exhibit interesting properties and biological activity themselves.^{496,522,523} For instance, the formamide moiety features as a key structural motif within various pharmaceuticals such as Leucovorin a chemotherapeutic agent, Formoterol which is used for the management of asthma/COPD and Orlistat prescribed to aid weight management (Figure 63).⁵²⁴⁻⁵²⁷ Additionally, *N*-formylpeptides

have been investigated as chemoattractants.^{516,528} By virtue of their Lewis basicity, formamides may successfully catalyse the allylation and hydrosilylation of carbonyl compounds as well as the transformation of carboxylic acids into acid chlorides.⁵²⁹⁻⁵³² Interestingly, formamides can function as formyl donors themselves and several species have been documented as stoichiometric formylating agents.^{496,533-535}

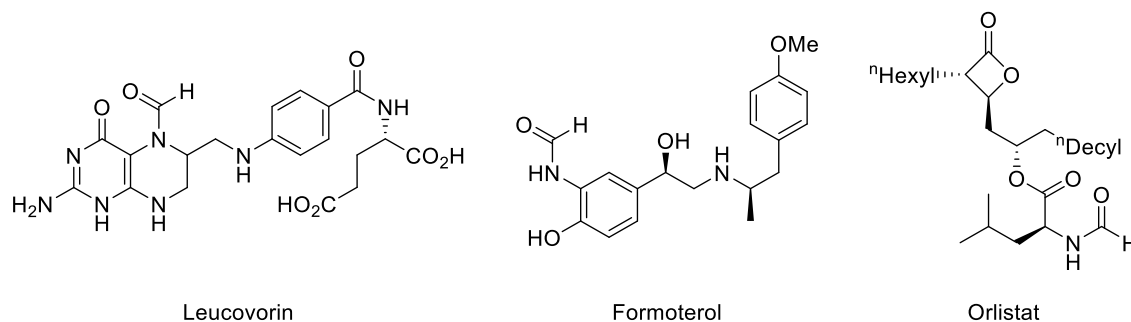


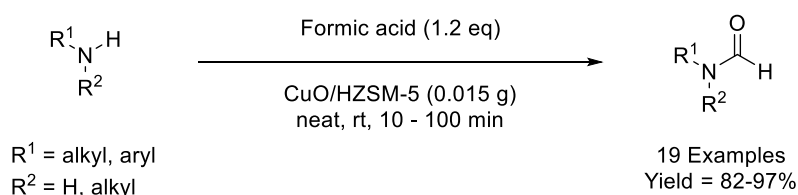
Figure 63. Active pharmaceuticals containing a formamide moiety.⁵²⁴⁻⁵²⁷

3.1.2 *N*-Formylating reagents

Due to the importance of the *N*-formyl moiety, numerous reagents and conditions have been developed for its installation.⁵³⁶ Methods for the *N*-formylation of amines was the subject of a recent comprehensive review by McElwee-White and Gerack.⁵³⁷ Therefore, only a brief overview is provided here. Historically, formylations were performed using formamide,⁵³⁸ chloral,⁵³⁹ triethyl orthoformate^{540,541} or formic acid.^{537,542} However, many of these reagents are only moderately reactive and thus require forcing conditions such as long reaction times, a large excess of reagent and elevated temperatures.^{496,514,543}

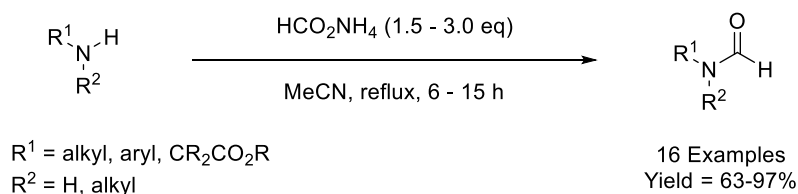
Nevertheless, due to its excellent atom efficiency, availability and low cost, the application of formic acid has been extensively investigated and a plethora of reagents and catalysts have been developed to promote this reaction.⁴⁹⁶ For instance, *N*-formylations with formic acid may be facilitated by the use of stoichiometric coupling reagents such as DCC,^{544,545} EDCI⁵⁴⁶ or CDMT.⁵⁴⁷ Alternatively, organic and non-metal based catalysts such as 2-chloro-4,6-dimethoxy[1,3,5]triazine/DMAP,⁵⁴⁷ iodine,⁵⁴⁸ sodium formate,⁵⁴⁹ melamine trisulfonic acid (MTSA),⁵⁵⁰ Amberlite IR-120,⁵⁵¹ thiamine hydrochloride,⁵⁵² 1,3,5-triazo-2,4,6-triphosphorine-2,2,4,4,6,6-hexachloride (TAPC),⁵⁵³ and ionic liquids^{536,554} have all been successfully applied. In many of these cases the catalytic effect can be attributed to the acidic nature of the species employed.⁵³⁷ An increasing number of metal catalysed formylations have also emerged within the literature, which encompasses elemental metals (e.g. Zn, In),^{555,556} Lewis acidic species such as ZnCl₂⁵⁵⁷ and also metal oxides (e.g. ZnO, MgO).⁵⁵⁸⁻⁵⁶¹ In an attempt to improve catalyst isolation and recyclability as well as efficiency, various solid-supported catalysts have also been investigated,⁵⁶² including: silica and alumina supported

catalysts,⁵⁶³⁻⁵⁶⁵ activated zeolites⁵⁶⁶⁻⁵⁶⁸ and clays.⁵¹⁵ Through implementing the various catalytic strategies outlined above, several examples have emerged that allow for *N*-formylations to be conducted using formic acid under mild, solvent free conditions with excellent efficiency and substrate scope.^{549,554,563,566-568} For instance, in 2016 Tajbakhsh *et al.* described that zeolite supported copper oxide nanoparticles could promote extremely rapid room temperature *N*-formylation of amines under solvent free conditions (Scheme 254).⁵⁶⁸ The corresponding formamides, including electron-deficient deactivated anilines, were isolated in excellent yields (82-97%).⁵⁶⁸ Alternatively, Das and co-workers have shown that the room temperature *N*-formylation of anilines may be achieved in the absence of a catalyst by performing the reaction in polyethylene glycol (PEG-400).⁵⁶⁹ Nevertheless, the use of toxic and corrosive formic acid may limit the applicability of these methods in an industrial context or in the presence of acid sensitive groups and typically requires the presence of a catalyst or forcing conditions.^{496,570,571}



Scheme 254. Solvent free, CuO/HZSM-5 catalysed *N*-formylation of amines using formic acid.⁵⁶⁸

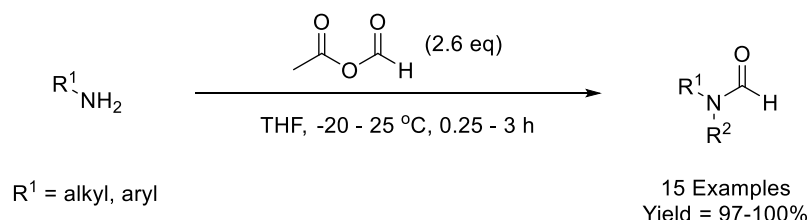
Formic acid derivatives have also been employed as stoichiometric formylating reagents.⁵⁷¹ Both ammonium formate and polymer supported tetraalkylammonium formate have been reported as effective reagents for accessing *N*-formyl species from the corresponding amino precursors.⁵⁷²⁻⁵⁷⁴ However, these salts exhibit similar activity to formic acid and thus require relatively forcing conditions. For example, to install an *N*-formyl group onto an amine or amino acid ester using ammonium formate, the mixture requires refluxing in acetonitrile for 6-15 hours (Scheme 255).^{573,574}



Scheme 255. *N*-Formylation of amines and amino acid esters using ammonium formate.^{573,574}

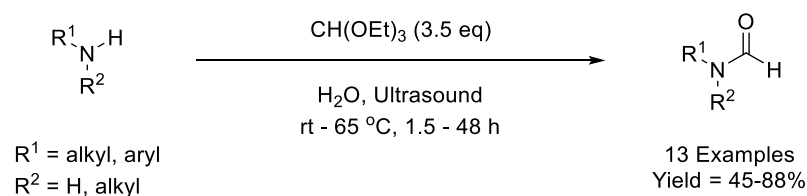
Alternatively, formic anhydride and mixed anhydrides, such as acetic formic anhydride, are more highly reactive derivatives and the latter is frequently utilised within organic synthesis.^{543,575-577} For instance, Krishnamurthy reported that a range of *N*-formyl compounds could be accessed in almost quantitative yields (97-100%) by treating the corresponding amines with acetic formic

anhydride at room temperature or below (Scheme 256).⁵⁷⁸ The main drawback associated with these reagents is their highly unstable nature and propensity to undergo hydrolysis.⁵⁴³ As formic anhydride cannot be isolated and acetic formic anhydride is known to decompose to acetic acid and carbon monoxide at room temperature, these reagents cannot be readily stored and must be generated *in situ* or prepared immediately prior to use.^{516,549,571,575}



Scheme 256. *N*-Formylation of primary amines using acetic formic anhydride.⁵⁷⁸

Trialkyl orthoformates represent a further class of stoichiometric formyl donors but have received comparatively little interest.^{531,540,579} Due to their moderate reactivity, these oxygen rich reagents again typically require heating or the presence of a Brønsted acid to promote successful *N*-formylation.^{531,540,579} Additionally, the preparation of trialkyl orthoformates from chloroform is undesirable.⁵⁷³ Recent research efforts have been focussed on developing milder procedures under aqueous conditions.^{531,540} For instance, in 2013 Habibi and co-workers examined the ultrasound promoted *N*-formylation of amines with triethyl orthoformate in water (Scheme 257).⁵⁴⁰ Whilst this method was applicable to a wide range of aromatic and benzylic amines and in some instances could be performed at room temperature, long reaction times and only moderate yields of the formamide products were isolated.⁵⁴⁰

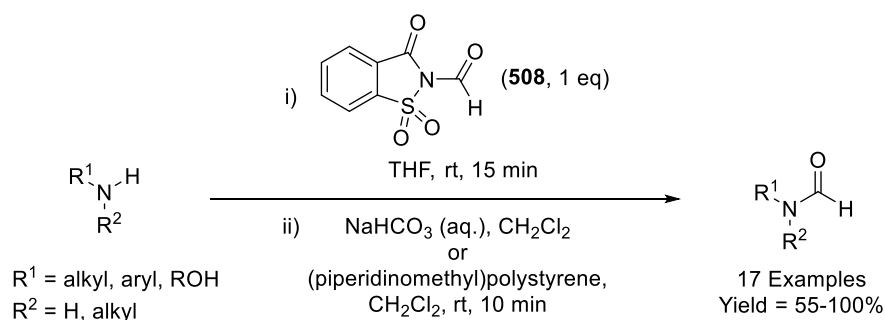


Scheme 257. Ultrasound promoted *N*-formylation of amines with triethyl orthoformate in water.⁵⁴⁰

More recently, research efforts have been focussed on developing transition metal catalysed *N*-formylation of amines *via* dehydrogenative reactions with methanol or paraformaldehyde,⁵⁸⁰⁻⁵⁸² carbonylation with CO⁵⁸³ or alternatively reductive functionalisation of CO₂.^{584,585} Whilst these methods provide high atom efficiency, they rely on the use of expensive metal catalysts and relatively forcing conditions.

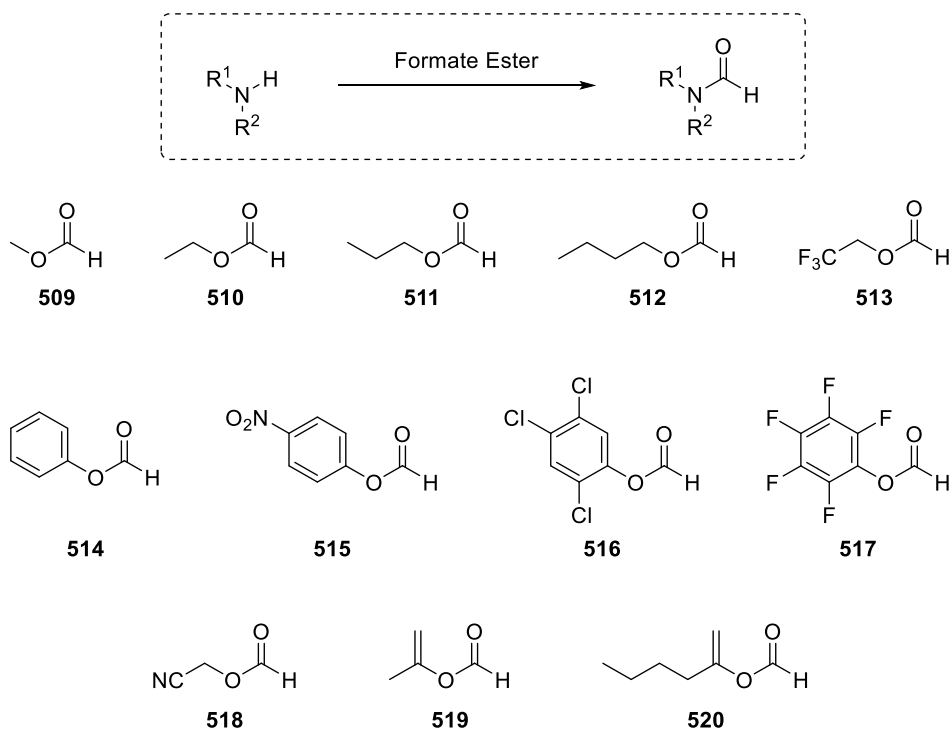
3.1.3 Formate esters and formamides as *N*-formylating reagents

Although typically the products of formylation reactions, formamides and formate esters also represent two alternative classes of stoichiometric formylating reagent. In this context, commercially available DMF and formamide have been utilised with heating and/or in the presence of various catalysts,^{524,534,586-588} whilst more elaborate *N*-formyl species have been developed to promote a facile reaction under milder conditions.⁵⁸⁹⁻⁵⁹¹ For example, Cossy and co-workers determined that the high yielding, chemoselective *N*-formylation of primary amines, secondary amines and amino alcohols could be achieved at room temperature in just 15 minutes using *N*-formylsaccharin **508** as the formyl donor (Scheme 258).⁵⁸⁹



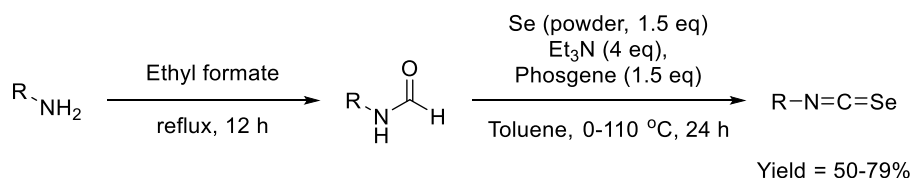
Scheme 258. Room temperature *N*-formylation of amines and amino acid esters using *N*-formylsaccharin **508**.⁵⁸⁹

In contrast to mixed anhydrides, formate esters are relatively stable and often do not require rigorously dry or inert conditions. Additionally, this approach typically allows for acidic conditions to be avoided. Scheme 259 summarises the formate esters that have been reportedly used as *N*-formylating reagents.



Scheme 259. Formate esters that have been employed as *N*-formylating reagents.

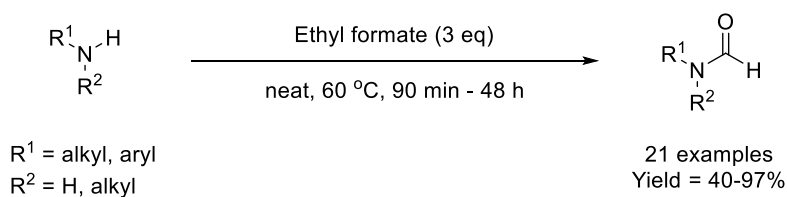
Commercially available, straight chain alkyl formate esters, such as methyl (**509**), ethyl (**510**), *n*-propyl (**511**) and *n*-butyl (**512**) formate have all been successfully applied within the synthesis of *N*-formyl species. Of these, inexpensive, non-toxic and non-corrosive ethyl formate (**510**) has been the most extensively investigated and is most commonly employed.^{496,570} Traditionally, the formylation of amines with ethyl formate (**510**) was simply achieved by refluxing the two components together, sometimes in the presence of catalytic quantities of a Brønsted acid.⁵⁹²⁻⁵⁹⁵ This methodology has since been applied within multi-step syntheses, where the formamide often features as a key intermediate.⁵⁹³⁻⁵⁹⁸ For instance, Barton *et al.* refluxed various amines with ethyl formate for 12 hours to synthesize a range of formamides, as the first step in the preparation of isoselenocyanates (Scheme 260).⁵⁹⁷ However, in addition to elevated temperatures, long reaction times are often required for formylations performed with ethyl formate (> 50 hours).^{547,593,594}



Scheme 260. Application of ethyl formate (**510**) methodology within the multistep synthesis of isoselenocyanates.⁵⁹⁷

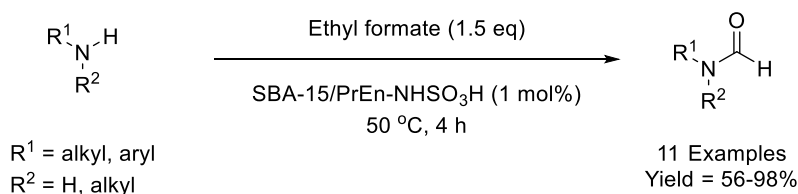
More recently, Bhanage *et al.* reported that a diverse range of formamides could be prepared by using a thermally promoted protocol, which is both solvent and catalyst free (Scheme 261).⁵⁰⁹

Excellent yields were obtained for numerous primary and secondary aliphatic amines (89-97%) and the methodology was also successfully applied to substituted anilines.⁵⁰⁹ Whilst various substituents conferring differing electronic effects were well tolerated in the *meta*- and *para*-positions (yield: 83-91%), the yield was often greatly degraded for *ortho*-substituted anilines, heterocyclic amines, such as 2-aminopyridine, and sterically encumbered diphenylamine even after extended reaction times (40-92%).⁵⁰⁹ As well as requiring elevated temperatures, a large excess of ethyl formate (3 equiv.) and re-optimisation of the reaction time was required to ensure satisfactory results.⁵⁰⁹



Scheme 261. *N*-Formylation of amines with ethyl formate (510) under catalyst and solvent free conditions.⁵⁰⁹

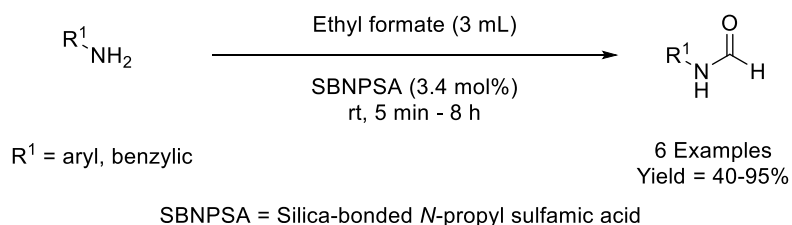
A series of heterogeneous catalysts have been developed to promote both *O*- and *N*-formylations with ethyl formate. In this context, solid supported Brønsted acids have been reported as effective catalysts.^{570,599} For instance, the group of Rostamnia prepared mesoporous silica bound sulfamic acid for amino formylations (Scheme 262).⁵⁹⁹ Significantly, good to excellent yields were achieved (82-98%) even for highly electron deficient aromatics using just 1 mol% catalyst loading in the absence of solvent at 50 °C.⁵⁹⁹ However, as in the previous example, sterically hindered diphenylamine gave a much reduced yield (56%).⁵⁹⁹ The authors demonstrated that there is the potential to recycle the catalyst; successfully employing it for 12 consecutive reactions without any detrimental effect.⁵⁹⁹



Scheme 262. Silica-supported sulfamic acid catalysed *N*-formylation of amines with ethyl formate (510).⁵⁹⁹

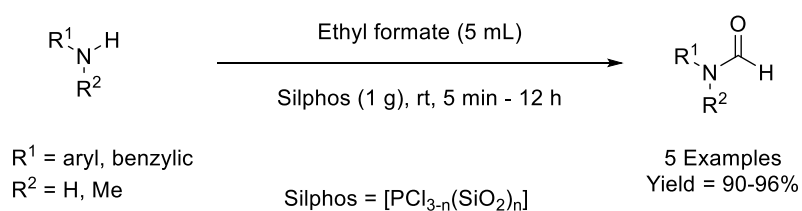
Niknam and co-workers reported an alternative recyclable, sulfamic acid based catalyst, which allowed for a room temperature variant of the formylation reaction to be developed (Scheme 263).⁵⁷⁰ Whilst primarily investigated for *O*-formylations, silica-bonded *N*-propyl sulfamic acid (SBNPSA) was found to promote the reaction of primary aliphatic and aromatic amines with ethyl formate under solvent free conditions in extremely short reaction times.⁵⁷⁰ With the exception of

strongly deactivated 4-nitroaniline, which was less reactive under the developed conditions, the reactions were high yielding (85-95%).⁵⁷⁰ A particular drawback of this methodology is the requirement for a large excess of the ethyl formate (3 mL), which is essentially functioning as both the reagent and solvent.⁵⁷⁰



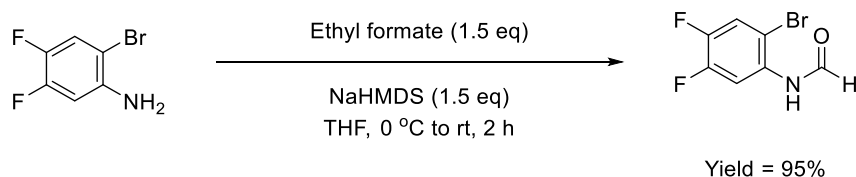
Scheme 263. Room temperature *N*-formylation of amines with ethyl formate (510) catalysed by SBNPSA.⁵⁷⁰

Silphos [$\text{PCl}_{3-n}(\text{SiO}_2)_n$], which is a heterogeneous phosphine-based species, has also been found to promote the room temperature formylation of alcohols and amines using ethyl formate (Scheme 264).⁶⁰⁰ From the small scope of amines examined by Iranpoor and co-workers, excellent yields of the *N*-formyl species were isolated (90-96%).⁶⁰⁰ Nevertheless, a large excess of Silphos (1 g / mmol of substrate) and ethyl formate (5 mL / mmol) were required.⁶⁰⁰



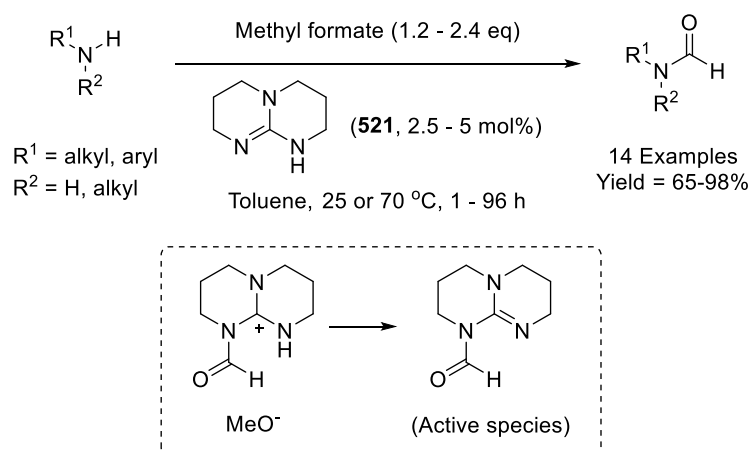
Scheme 264. Silphos catalysed *N*-formylation of amines with ethyl formate (510).⁶⁰⁰

Interestingly, Wang *et al.* detailed that 2-bromo-4,5-difluoroaniline could be transformed into the corresponding formamide in high yield (95%) after 2 hours by treatment with sodium bis(trimethylsilyl)amide (NaHMDS) at 0 °C and subsequent addition of ethyl formate (Scheme 265).⁶⁰¹ However, this methodology has not been systematically examined for a range of amine substrates.⁶⁰¹



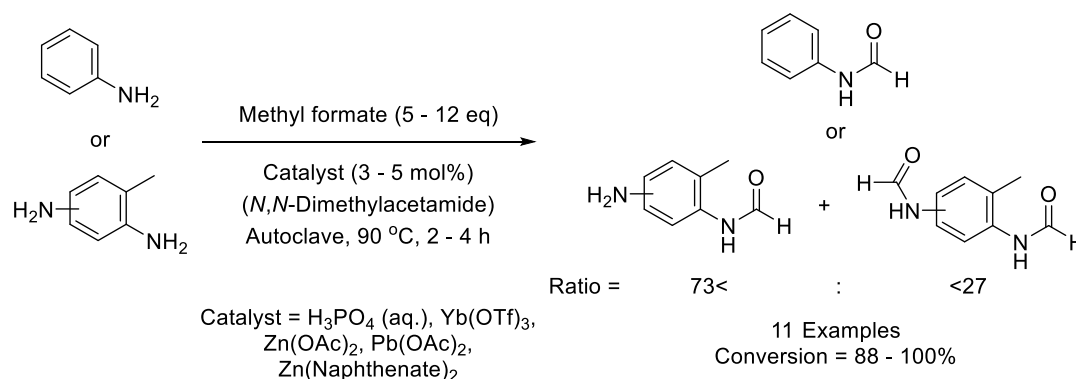
Scheme 265. Base promoted *N*-formylation of amines with ethyl formate (510).⁶⁰¹

Recently, methyl formate (**509**) has received increasing interest as a less costly formyl donor.^{496,514} For instance, in 2009 bicyclic guanidine base **521** was identified by Deutsch *et al.* as an exceptionally active organocatalyst for the high yielding (65-98%), room temperature formylation of primary, secondary aliphatic and aromatic amines with methyl formate (Scheme 266).⁵¹⁴ For strongly nucleophilic amines the formylation was conducted with only 1.2 equivalents of methyl formate and a 2.5 mol% catalyst loading of **521** in toluene.⁵¹⁴ However, aromatic amines and more sterically encumbered aliphatic species required a greater excess of formylating reagent (2.4 equiv.) under solvent free conditions and/or a higher catalyst loading (5 mol%).⁵¹⁴ Extended reaction times of up to 96 hours were also necessary in some instances and the reactions of electron deficient anilines were met with limited success, despite being performed at 70 °C in an autoclave.⁵¹⁴ Interestingly, this methodology relies on the *in situ* formation of an *N*-formylated guanidinium cation as the active formylating species.⁵¹⁴



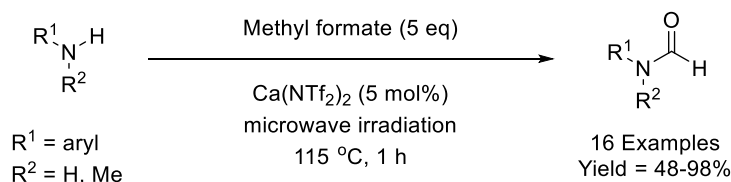
Scheme 266. Bicyclic guanidine base catalysed *N*-formylation of amines with methyl formate (**509**).⁵¹⁴

A patent published by BASF in 2014 reported that formamides, derived from both primary and secondary aromatic amines, could be synthesized using methyl formate accompanied by catalytic quantities of phosphoric acid or Lewis acidic zinc, lead and ytterbium salts (Scheme 267).^{496,602} Specifics were only provided for aniline and diaminotoluene derivatives, for which high conversion was typically achieved.^{496,602} However, some starting material still remained and for the diamino derivative both bis- and mono-formylation was observed.^{496,602} Performing the reactions with heating under autogenous pressure allowed for reaction times to be reduced to a few hours (2-4 h), however a large excess of the formate ester was still necessary irrespective of the catalyst system (~5 equiv.).^{496,602}



Scheme 267. Phosphoric acid and Lewis acid promoted *N*-formylation of anilines with methyl formate (509).⁶⁰²

Most recently, Corbet *et al.* developed a calcium (and hydrogen) triflimide catalysed protocol for the formylation of anilines using methyl formate under microwave irradiation; affording the corresponding formamides in moderate to excellent yields (48-98%) (Scheme 268).⁴⁹⁶ As is frequently reported, more poorly nucleophilic anilines furnished with electron withdrawing groups and *ortho*-substituted species gave the inferior results.⁴⁹⁶ In particular, 4-nitroaniline was not readily amenable to this methodology.⁴⁹⁶ Whilst introduction of the formyl group was universally rapid (1 h), relatively forcing conditions were required (115 °C, 5 equiv. methyl formate).⁴⁹⁶

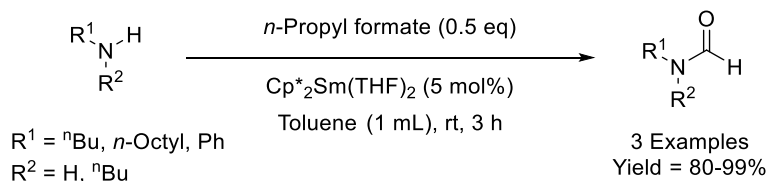


Scheme 268. Calcium triflimide catalysed *N*-formylation of anilines with methyl formate (509).⁴⁹⁶

Sporadic reports exist within the literature of methyl formate being applied as the formylating reagent within multi-step syntheses.^{496,514,603-605} Typically, these reactions are uncatalysed and involve highly nucleophilic amines but suffer from long reaction times, require a large excess of reagent and/or require elevated temperatures.^{496,514,603-605} It is interesting to note that, among other methods, DMF is manufactured on an industrial scale from the combination of dimethylamine and methyl formate in a reactive distillation column.^{496,606}

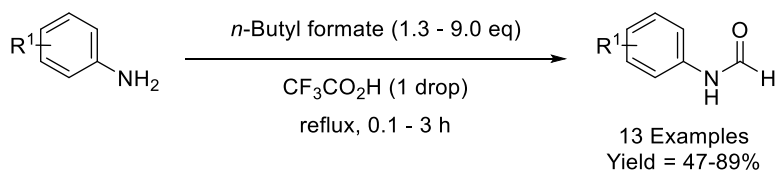
In 1996, Ishii and co-workers determined that $\text{Cp}^*_2\text{Sm}(\text{THF})_2$ was not only an effective catalyst for acylation reactions but also for the formylation of amines with *n*-propyl formate (**511**) in toluene (Scheme 269).⁶⁰⁷ For the limited scope of amines examined, namely aniline, octylamine and dibutylamine, high yields (80-99%) were achieved.⁶⁰⁷ Whilst it was possible to perform the

reaction at room temperature, the amine was required in a 2-fold excess relative to the formate ester.⁶⁰⁷



Scheme 269. Samarium catalysed *N*-formylation of amines with *n*-propyl formate (511).⁶⁰⁷

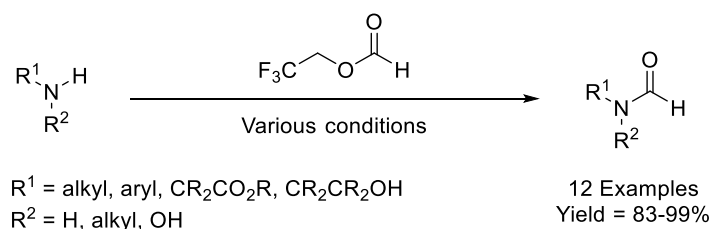
Using chain extended *n*-butyl formate (**512**), Daszkiewicz *et al.* reported that substituted anilines could be successfully formylated under reflux in the presence of catalytic quantities of trifluoroacetic acid (Scheme 270).⁵⁰¹ Whilst this method benefits from short reaction times (0.1 – 3 hours) and is run in the absence of solvent, reoptimisation was necessary for each substrate and often a large excess of formate ester was required to achieve satisfactory conversion (1.3 – 9.0 equiv.).⁵⁰¹ Both electron rich and electron deficient anilines were amenable to this methodology and, with the exception of sterically crowded 2,6-dimethylaniline (47%), good yields were achieved (63-89%).⁵⁰¹



Scheme 270. Acid catalysed *N*-formylation of anilines with *n*-butyl formate (512).⁵⁰¹

In 2002 Hill and co-workers established that 2,2,2-trifluoroethyl formate (**513**), which is commercially available or may be simply prepared by the treatment of 2,2,2-trifluoroethanol with formic acid, is an extremely versatile formylating reagent.⁶⁰⁸ The authors successfully applied this reagent to the selective *N*-formylation of amines, amino alcohols, amino acid esters and quite exceptionally hydroxylamines as well as the *O*-formylation of alcohols (Scheme 271).⁶⁰⁸ Although only a small range of substrates were examined for each class of compound, good yields were universally achieved.⁶⁰⁸ Both the representative primary and secondary aliphatic amine were formylated in excellent yield (94 and 99% respectively) after just 1 hour at room temperature using a small excess of reagent (1.1 equiv.).⁶⁰⁸ However, primary aromatic amines (yields: 83% and 99%), an amino alcohol (yield: 97%) and amino acid esters (yield: 92-95%) required individual re-optimisation and more forcing conditions to achieve appreciable conversion.⁶⁰⁸ This included any combination of: heating the reaction (65 °C), employing a large excess of reagent (up to 10 equiv.), adding formic acid (10 wt%) as an additive and leaving the reaction for an extended period of time (up to 24 hours).⁶⁰⁸ Significantly, 2-nitroaniline was successfully

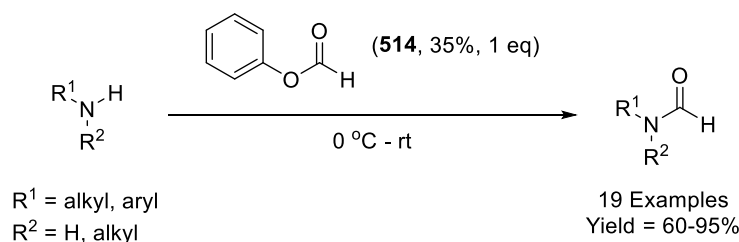
formylated in high yield (83%) by employing these tactics.⁶⁰⁸ The high yielding (88-95%) and *N*-selective formylation of hydroxylamines was achieved at elevated temperatures, using a large excess of 2,2,2-trifluoroethyl formate (5-10 equiv.), which in some instances contained formic acid (10 wt%) to convert any of the undesired *O*-formyl isomer into the *N*-formyl species.⁶⁰⁸ Again, the exact conditions required were found to be substrate dependent.⁶⁰⁸



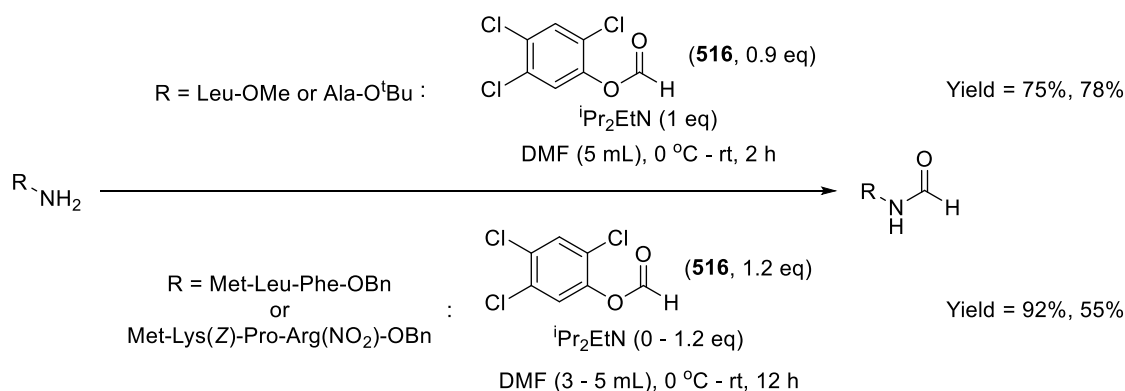
Scheme 271. *N*-Formylation with 2,2,2-trifluoroethyl formate (513).⁶⁰⁸

To date, only a small handful of more elaborate activated formate esters have been prepared and implemented as successful formylating reagents. Typically, these formate esters must be synthesized prior to use and as with other organic formyl carriers unavoidably produce stoichiometric quantities of waste.⁵¹⁴ Despite the reduced atom efficiency of this method, these reagents are valuable alternatives as they are typically more highly reactive.⁵¹⁴ As such, milder reaction conditions may be employed, which avoid the need for a catalyst.^{514,557}

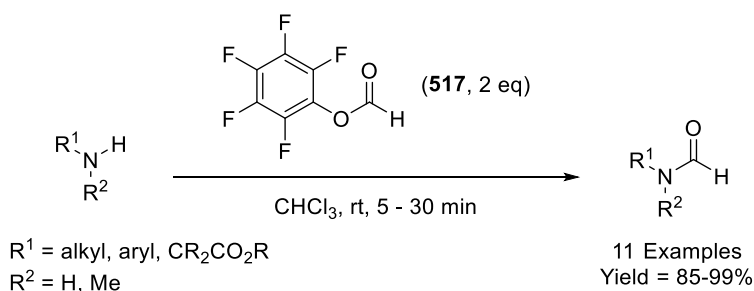
For instance, aromatic formate esters, namely phenyl formate (**514**), 4-nitrophenyl formate (**515**), 2,4,5-trichlorophenyl formate (**516**) and pentafluorophenyl formate (**517**) have all been reported to function as formylating reagents at room temperature.^{517,609,610} These reagents are typically synthesized from the formylation of the parent phenol with formic acid under varying conditions.^{517,609,610} Due to difficulties encountered in its isolation, phenyl formate was typically employed as a crude mixture containing significant quantities of phenol (up to 60%).⁶⁰⁹ Nevertheless, good to excellent yields of both primary and secondary amines (60-95%) were achieved, without the need for excess phenyl formate (Scheme 272).⁶⁰⁹ Most significantly this method was applicable to heterocyclic amines, such as aminopyridine and aminopyrimidine derivatives, as well as mildly electron deficient anilines.⁶⁰⁹ Interestingly, this methodology was extended to the formylation of amidoximes, with protection of the {NH₂} moiety of *p*-nitrobenzamidoxime generating the corresponding formamide in good yield (85%).⁶⁰⁹

Scheme 272. *N*-Formylation of amines with phenyl formate (**514**).⁶⁰⁹

515 and **516** were specifically applied to the synthesis of a select few *N*-formyl amino acid esters and *N*-formyl peptides (Scheme 273).⁵¹⁷ Whilst both species were found to be reactive towards amine nucleophiles, 2,4,5-trichlorophenyl formate (**516**) was found to be more highly stable and yields provided were attained using this reagent.⁵¹⁷ *N*-Formyl-L-leucine methyl ester and *N*-formyl-L-alanine *tert*-butyl ester were synthesized in 75% and 78% yield respectively from the corresponding amino acid esters in 2 hours, with the substrate in slight excess relative to the formylating reagent.⁵¹⁷ The *N*-formylation of peptides required longer reaction times (12 hours) but moderate to excellent yields were achieved (55 and 92%).⁵¹⁷

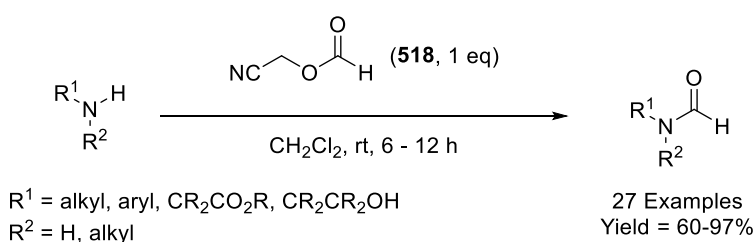
Scheme 273. *N*-Formylation of amino acid esters and peptides with 2,4,5-trichlorophenyl formate (**516**).⁵¹⁷

Kisfaludy *et al.* subsequently determined that a 1 mol excess of pentafluorophenyl formate (**517**) could promote extremely rapid (5-30 min) and chemoselective *N*-formylation of primary amines, encompassing aliphatic, aromatic, amino acid esters and *O*-protected peptides; affording the corresponding formamides in excellent yields (85-99%) (Scheme 274).⁶¹⁰ However, pentafluorophenyl formate is particularly unstable and was found to decompose at a rate of 25% per week at room temperature or 10% per week at $4\text{ }^{\circ}\text{C}$.^{587,610} Interestingly, a one pot synthesis of the reagent and subsequent formylation was developed and successfully applied to the *N*-formylation of an ester protected peptide; providing the *N*-formyl species in 97% isolated yield (*cf.* 99% yield step-wise).⁶¹⁰



Scheme 274. *N*-Formylation of amines, amino acid esters and peptides with pentafluorophenyl formate (**517**).⁶¹⁰

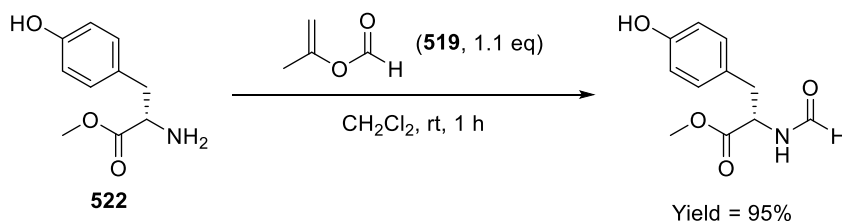
Niclas and co-workers determined that cyanomethyl formate (**518**), which can simply be prepared in one step from chloroacetonitrile by heating with potassium formate in sulfolane, successfully installs an *N*-formyl group onto primary amines, secondary amines and amino acid esters (Scheme 275).^{497,611,612} Such reactions were conducted at room temperature in dichloromethane using equimolar quantities of **518** in the absence of a catalyst.^{497,611,612} This reagent was found to be chemoselective; affording exclusively the *N*-formylated product of ethanolamine and serine.^{497,611,612} Formamides derived from primary and secondary amines were furnished in good yields (60-81%) after just 6 hours, whilst the formylation of amino acid ester hydrochlorides generated good to excellent yields (62-97%) of essentially enantiopure ($ee \geq 99\%$) material after 12 hours.^{497,611,612} Interestingly, *tert*-butyl amino acid esters were amenable to this methodology, which is often found to be incompatible with formic acid and acetic anhydride.^{497,611,612} Poorly nucleophilic nitroanilines as well as alcohols were successfully protected at 75 °C but required the presence of catalytic quantities of imidazole.^{497,611,612} However, cyanomethyl formate and the stoichiometric by-product are highly toxic and a halogenated solvent was employed.⁵⁸⁷



Scheme 275. *N*-Formylations using cyanomethyl formate (**518**).^{497,611,612}

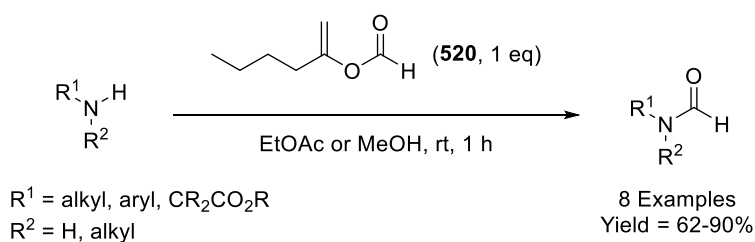
Enol formates **519** and **520** have also been found to function as formyl donors.^{516,521} Interestingly, formylations performed using these species are entirely irreversible, as a ketone rather than an alcohol is generated as the by-product.^{501,516,521} An equilibrium between the formylating reagent and formylated product is therefore avoided. Initial work by van Melick and Wolters highlighted the potential of isopropenyl formate **519** to function as a facile *N*-formylating reagent for primary

and secondary amines as well as for the selective amino formylation of amino acid esters, such as **522**, under neutral conditions (Scheme 276).⁵²¹



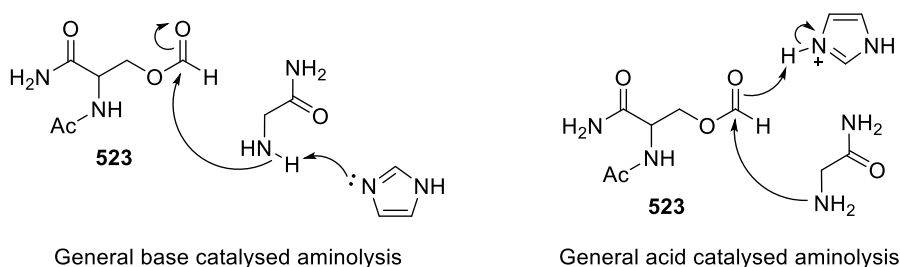
Scheme 276. *N*-Formylation of L-tyrosine methyl ester (**522**) with isopropenyl formate (**519**).⁵²¹

Prompted by the success of this reagent, in 1991 Dixneuf and co-workers addressed the unfavourable multistep synthesis required to prepare the enol formate reagent.⁵¹⁶ Specifically, a ruthenium catalysed cross coupling of formic acid with terminal alkynes was developed; allowing for the direct synthesis of **519** from propyne as well as structurally related species **520** from 1-hexyne.⁵¹⁶ The authors detailed that both enol formates provided a very rapid transfer of their formyl group to primary and secondary amines when combined in ethyl acetate for one hour at ambient temperature.⁵¹⁶ A small sample of substrates were examined and good to excellent yields of the formamides were attained (62-90%), with yields quoted for reactions performed using the hex-1-en-2-yl derivative **520** (Scheme 277).⁵¹⁶ In relation to operational simplicity, it is noteworthy that isopropenyl formate **519** may be employed as the crude derivative.⁵¹⁶ Extension of this methodology to the ethyl ester derivatives of amino acids was met with similar success; generating the *N*-formyl species in good yields (70-71%) when conducted in methanol.⁵¹⁶



Scheme 277. *N*-Formylation of amines and amino acid esters with hex-1-en-2-yl formate (**520**).⁵¹⁶

Although *N*-acetyl-*O*-formylserinamide **523** has not been systematically investigated for the *N*-formylation of amines, general base catalysed aminolysis of this species is known to be more facile and proceed at a higher rate than aminolysis of methyl formate (Scheme 278).⁶¹³



Scheme 278. Imidazole catalysed aminolysis of *N*-acetyl-*O*-formylserinamide (**523**).⁶¹³

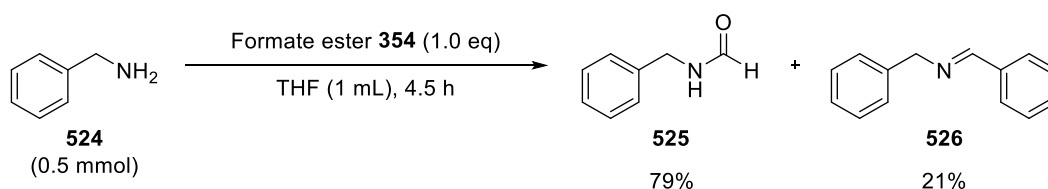
3.2 Project aims

Whilst numerous procedures have been published for the *N*-formylation of amino functionality, the pursuit of more effective reagents and milder reaction conditions remains the focus of current research efforts. Based on the high reactivity of formate esters and their reported success in affecting room temperature and catalyst free *N*-formylations,⁵¹⁴ the application of readily accessible **354** as a formyl donor for the synthesis of formamides was of interest. It was anticipated that fragmentation of this formylating reagent into a number of stable by-products upon reaction with a nucleophile may provide a driving force for the desired reaction; allowing for short reaction times and mild conditions to be employed.⁶¹³ As formate ester **354** is an oil and does not produce toxic by-products, it was hoped that a greener protocol may be developed; avoiding the use of undesirable organic solvents, which are typically employed with other formate esters.^{428,553} Such a method would also provide an alternative to mixed anhydrides, which are highly unstable,^{516,549} and formic acid, which typically requires forcing conditions or the use of a catalyst.^{496,514} Additionally by avoiding toxic and corrosive formic acid, such a method may be amenable to acid sensitive functional groups.^{496,570,610}

3.3 Results and Discussion

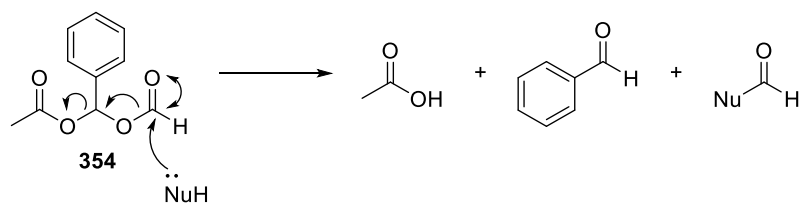
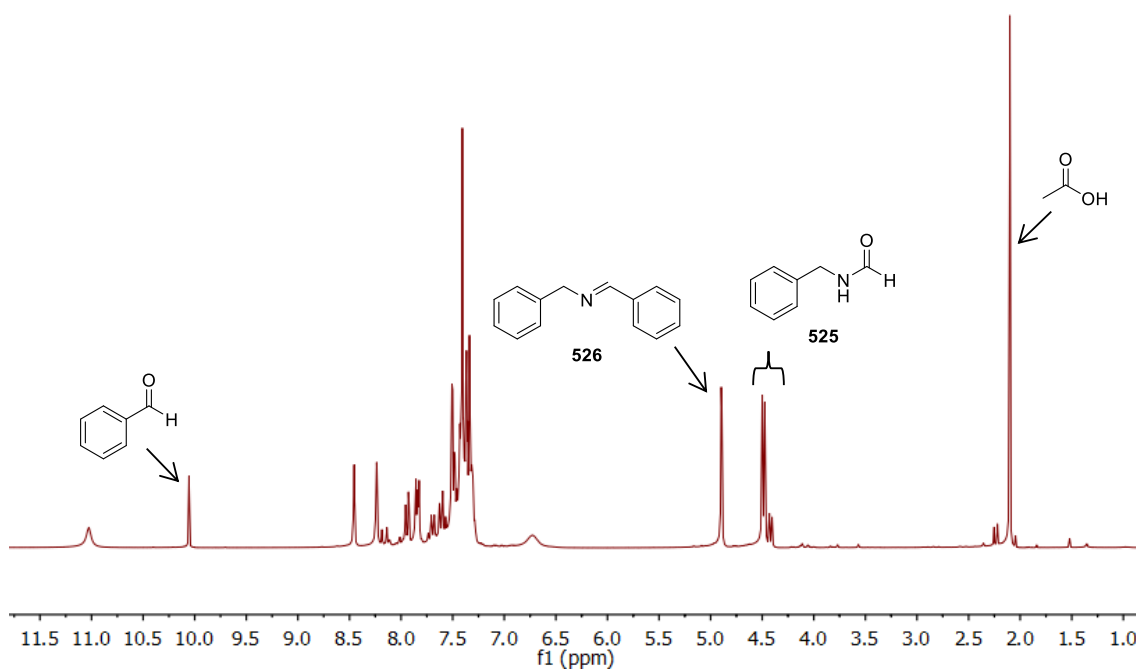
3.3.1 Development of *N*-formylation methodology using (formyloxy)(phenyl)methyl acetate

A method for the direct *N*-formylation of amines to generate formamides was initially targeted. The formylation of benzylamine (**524**), a simple primary amine, was studied to establish the reactivity of formate ester **354**. This species was examined as the model compound due to its relatively high nucleophilicity and distinctive benzylic protons, which allowed for simplified analysis. More specifically, benzylamine was added in a single portion to a THF solution of formate ester **354** (1.0 equiv.) and the resulting mixture was stirred at room temperature for 4.5 hours (Scheme 279). The crude mixture was then concentrated *in vacuo* using a water bath at ambient temperature and immediately analysed by ^1H NMR spectroscopy, with the spectrum obtained in deuterated chloroform. Pleasingly, complete consumption of benzylamine was observed, as evidenced by the absence of a characteristic singlet at 3.87 ppm for the benzylic protons. Further analysis of the ^1H NMR spectrum revealed the presence of two species. The expected formamide **525** was observed as a mixture of rotamers, which exhibited downfield shifts of 4.42 ppm and 4.49 ppm for the minor and major rotamers respectively, alongside 21% of imine **526**, as deduced from the distinctive singlet at 4.89 ppm.^{614,615} The relative ratio of such species was determined by comparison of the relative integrals for each of these characteristic peaks.

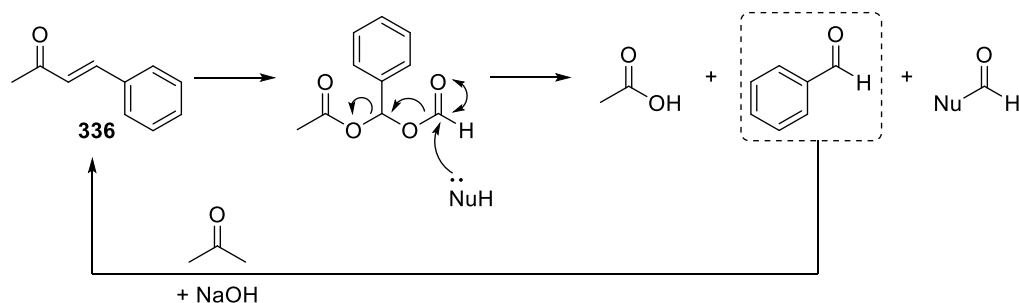


Scheme 279. Examining the *N*-formylation of benzylamine (**524**) with formate ester **354**.

Mechanistically, it is proposed that the amine nucleophile attacks the formyl group of (formyloxy)(phenyl)methyl acetate (**354**), to afford the desired formamide, whilst generating benzaldehyde and acetic acid as by-products (Scheme 280). The presence of acetic acid and benzaldehyde in the crude reaction mixtures, as deduced from the singlets at 2.10 and 10.06 ppm respectively within the ^1H NMR spectrum, helps corroborate such a mechanism (Figure 64).^{616,617} Interestingly, competitive acylation of the amine *via* nucleophilic attack of the acyl moiety of **354**, was not observed. A representative spectrum for the formylation of benzylamine is given in Figure 64, highlighting each of the key reaction species.

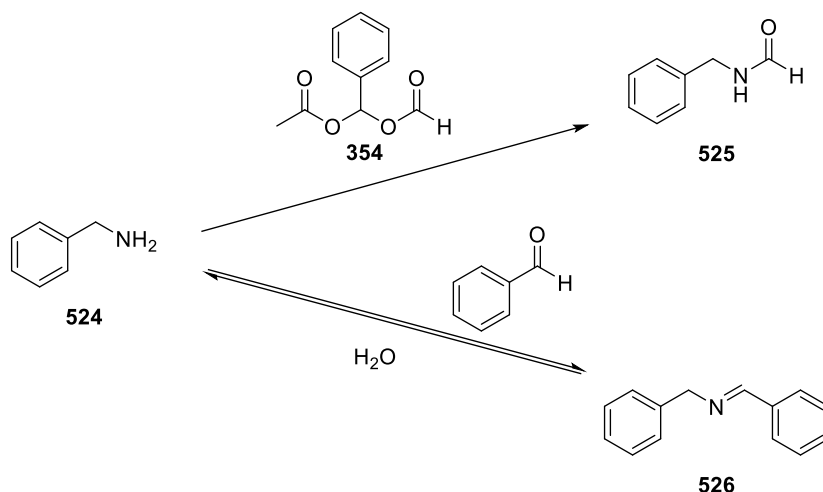
Scheme 280. Proposed mechanism for the reaction of formate ester **354** with nucleophiles.Figure 64. Representative 250 MHz ^1H NMR spectrum obtained in CDCl_3 for the crude formylation reaction mixture (formylation of benzylamine (**524**) with formate ester **354**).

The described fragmentation is proposed to act as an entropic driving force for the reaction and the formylation may also be aided by the stability of the resulting by-products.⁶¹³ Furthermore, as previously detailed for enol formates **519** and **520**,^{516,521} avoiding the generation of an alcohol by-product allows for the desired transformation to be completely irreversible. Despite the favourable entropy associated with fragmentation of **354**, hydrolysis with atmospheric moisture was found to be comparatively slow.⁵⁷¹ The formylating reagent was stable for a number of weeks at room temperature before degradation started to occur. Storage at a cooler temperature would be anticipated to preserve the formylating reagent for a far extended period of time. Nevertheless, samples of partially degraded material were still found to be effective at formylating the amine. Whilst the formation of multiple by-products isn't ideal, it is conceivable that the benzaldehyde may be recycled as a feedstock for the production of the α,β -unsaturated ketone **336**, which is used for the synthesis of the formylating reagent; thus reducing waste (Scheme 281).



Scheme 281. Potential method of recycling the benzaldehyde by-product.

Imine **526** is formed from the condensation of benzylamine with *in situ* generated benzaldehyde; a process that is competitive with the desired formylation (Scheme 282). As imine bond formation is reversible and imine **526** should be susceptible to hydrolysis, it was hypothesized that the equilibrium could be shifted further in favour of the amine starting material **524** by the addition of water. Crucially, as the formylation of benzylamine is irreversible, perturbing the equilibrium towards this species should consequently improve conversion to formamide **525**.

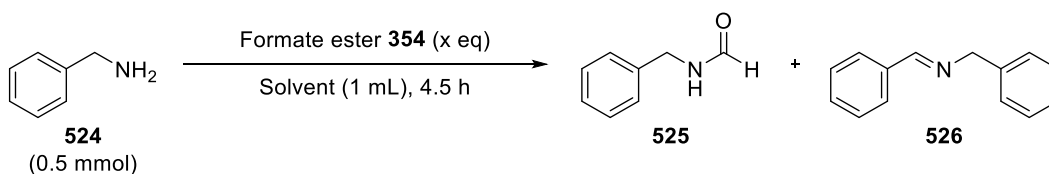


Scheme 282. Competitive reactions of benzylamine (**524**): i) desired *N*-formylation with formate ester **354**, ii) reversible imine formation with the benzaldehyde by-product.

Therefore, in an attempt to improve the selectivity of the reaction for the desired formamide **525**, the reaction was performed in a 1:1 solution of THF:water (Table 32, entry 2). Pleasingly, in the presence of water the selectivity for formamide **525** was slightly improved from 79% to 86% (Table 32, entries 1 and 2). As benzylamine (**524**) can either undergo condensation with benzaldehyde or formylation by reaction with **354**, it was postulated that increasing the amount of formylating reagent may enhance the rate of the desired reaction and further improve selectivity (Table 32, entries 3 and 4). A similar degree of improvement was observed for both the non-aqueous reaction and the formylation performed in the presence of water, with 99%

selectivity achieved with 1.5 equivalents of formylating reagent in a 1:1 THF:water solution (Table 32, entry 4).

Table 32. Examining the selectivity of the *N*-formylation of benzylamine (524**) with varying amounts of formate ester **354** and water.**



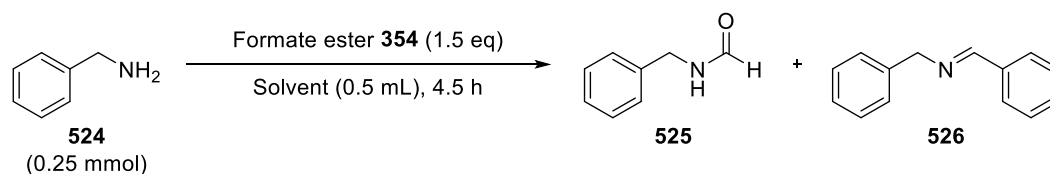
Entry	Formate ester 354 (equiv.)	Solvent	Formamide 525 ^a	Imine 526
1	1.0	THF	79	21
2	1.0	THF:H ₂ O (1:1)	86	14
3	1.5	THF	90	10
4	1.5	THF:H ₂ O (1:1)	99	1

^aProduct ratios were determined by ¹H NMR spectroscopic analysis.

Based on the success of this solvent system in minimising the level of imine contamination, a comprehensive solvent screen was conducted, with an emphasis on identifying a suitable green solvent (Table 33).^{428,429} Specifically, solvents exhibiting a range of polarities, as well as biphasic systems were explored. With the exception of ethanol and 1,4-dioxane (Table 33, entries 2 and 6), only trace amounts of the imine **526** were observed (<4%). Thus, it may be deduced that ethers and alcohols promote formation of the imine and are unsuitable for this methodology. It is notable that no discernible trend relating to solvent polarity and product distribution was observed. From a green chemistry perspective, the success of the solvent free reaction and those performed in ethyl acetate and water were of particular interest (Table 33, entries 1, 5 and 10),^{428,429} which were all repeated on a slightly larger 1 mmol scale (conversions shown in parentheses). For the latter, it is debatable whether the reaction is actually occurring within the solvent or just at the surface, as many of the reagents are relatively insoluble and in liquid form. Nevertheless, this is an extremely exciting result as many formylating reagents are susceptible to hydrolysis and therefore cannot be applied to reactions that require aqueous media, such as the formylation of unprotected amino acids.⁶¹⁸ Additionally, this finding indicates that the reaction may be compatible with a buffered solution, which may circumvent any issues arising from the generation of acetic acid. However, due to the insolubility of many substrates in water and the problems associated with its removal, it was not pursued any further within the *N*-formylation of amines. Developing a solvent free protocol was considered favourable in part due to its green chemistry credentials but also due

to the exceptional selectivity achieved for the formamide (100%). For the formylation of solid amines, ethyl acetate was considered a viable alternative based on similar considerations.

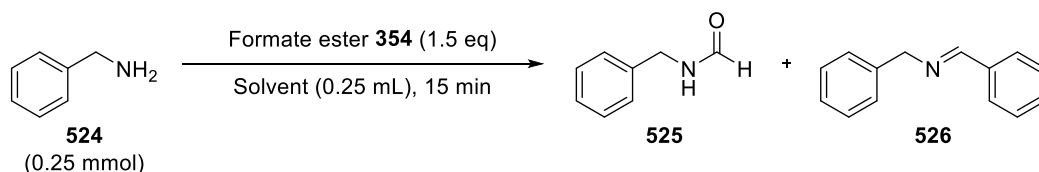
Table 33. Solvent screen for the reaction of benzylamine (**524**) with formate ester **354**.



Entry	Solvent	Formamide 525 ^a	Imine 526
1	H ₂ O	100 (97 ^b)	- (3 ^b)
2	EtOH	88 ^b	12 ^b
3	MeCN	96	4
4	MeCN:H ₂ O (1:1)	100	-
5	EtOAc	98 (97 ^b)	2 (3 ^b)
6	1,4-Dioxane	92	8
7	1,4-Dioxane:H ₂ O (1:1)	99	1
8	CH ₂ Cl ₂	100	-
9	PhMe	100 (100 ^b)	-
10	Neat	98 (100 ^b)	2 (- ^b)

^aProduct ratios were determined by ¹H NMR spectroscopic analysis. ^b1 mmol scale.

In order to assess the rate of formylation both in the absence and presence of solvent, the reaction of benzylamine under the conditions outlined in entries 5 and 10 of Table 33 was repeated for 15 minutes (Table 34). Interestingly, it was determined that complete consumption of the amine starting material had already occurred under both conditions but relatively large quantities of imine **526** were present in the samples. In conjunction with the high selectivity observed for **525** after 4.5 hours, this finding demonstrates that the imine slowly decomposes back to the amine over time; allowing for its irreversible formylation to occur. Slightly better selectivity for formamide **525** was again observed in the solvent free reaction (Table 34, entry 2).

Table 34. Examining the conversion and product distribution for the reaction of benzylamine (524**) with formate ester **354** after 15 minutes.**

Entry	Solvent	Formamide 525 ^a	Imine 526
1	EtOAc	87	13
2	Neat	93	7

^aProduct ratios were determined by ¹H NMR spectroscopic analysis.

In order to examine the extent and reversibility of imine formation, in particular the rate of its depletion, kinetic profiling by ¹H NMR spectroscopy was performed. The reaction of benzylamine with (formyloxy)(phenyl)methyl acetate (**354**) in deuterated toluene was monitored by ¹H NMR spectroscopy, with scans being performed at five minute intervals over a two hour period (Figure 65). Deuterated toluene was identified as a suitable solvent, as reasonable amounts of imine were found to form initially but the reaction provides quantitative conversion to the formamide over time (Table 33, entry 9). As can be determined from the ¹H NMR overlays, after 15 minutes 14% of the benzylamine had reacted to form imine **526** with the rest existing as formamide **525**. The amount of imine steadily decreases over time, with less than 1% remaining after 1 hour and essentially complete conversion to the formamide after 2 hours. Therefore, subsequent reactions were performed for 1 hour.

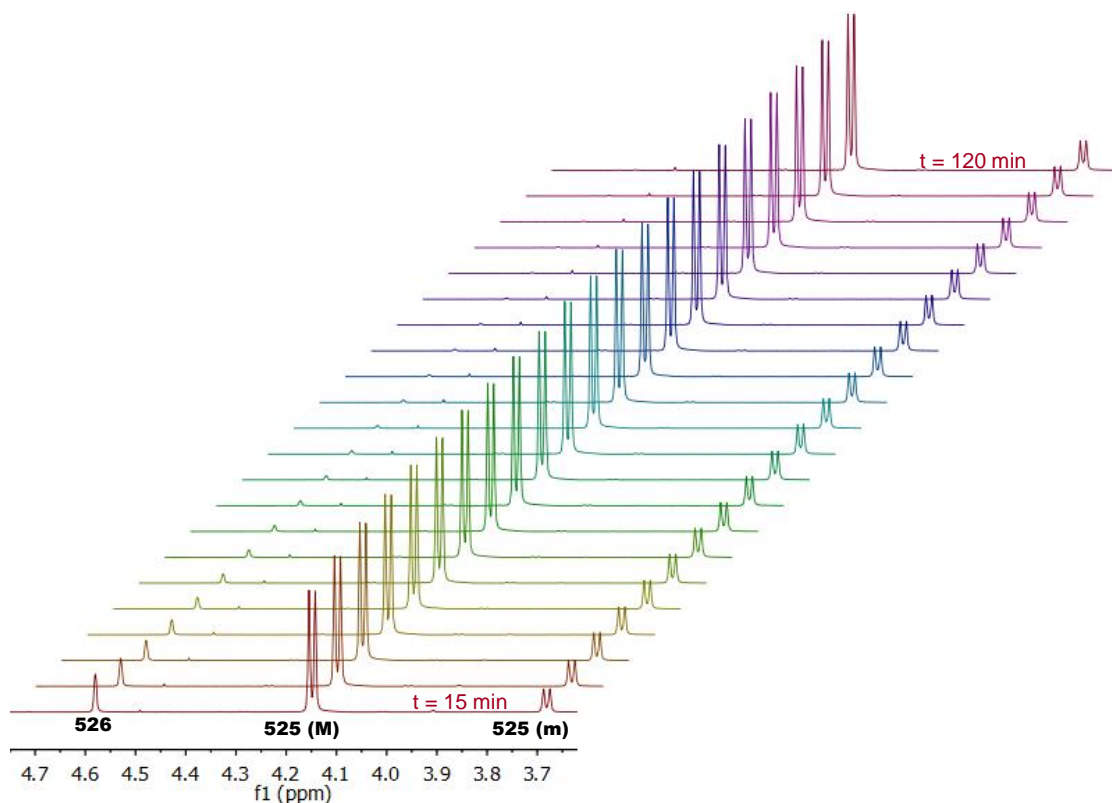


Figure 65. Kinetic profiling by ^1H NMR spectroscopy for the reaction of benzylamine (**524**) with formate ester **354** (1.5 equiv.). Acquisitions were performed at 5 minute intervals over an 120 minute period commencing at 15 minutes. Major and minor rotamers are denoted by (M) and (m) respectively.

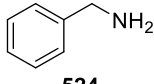
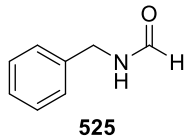
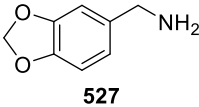
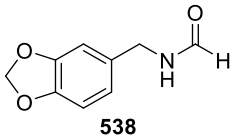
3.3.2 Scope of primary and secondary amines

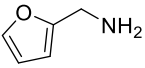
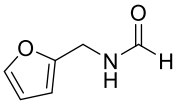
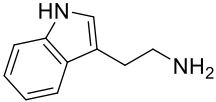
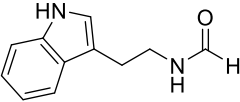
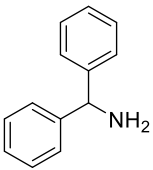
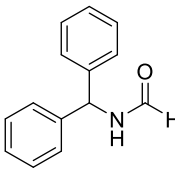
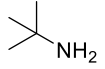
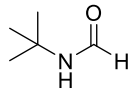
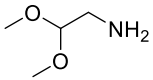
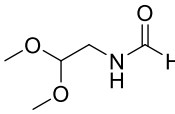
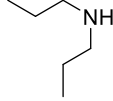
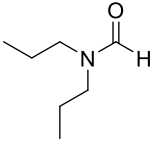
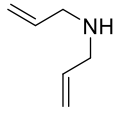
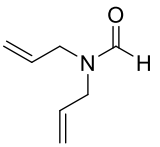
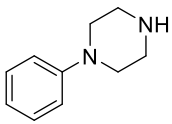
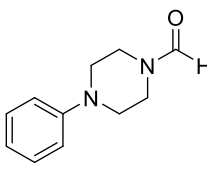
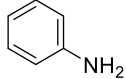
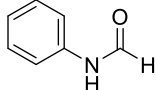
To examine the substrate generality and assess the reactivity of **354**, the developed methodology was applied to a diverse range of primary and secondary (aliphatic and aromatic) amines (Table 35 and Table 36). The appropriate amine was simply treated with 1.5 equivalents of neat formylating reagent at room temperature or in instances where the amine was solid or the reaction solidified an ethyl acetate solution was employed. Interestingly, upon addition of the amine substrate to the formate ester a mild exotherm and fuming was noted in many instances, with the mixture also developing a pink hue on occasions. It was possible to immediately purify the crude residues by flash column chromatography upon removal of any solvent, without the need for prior work-up. Any co-eluted acetic acid was effectively removed under reduced pressure as an azeotrope with toluene. The structures of the isolated, analytically pure formamides were confirmed by comparison of their spectroscopic data with that reported in the literature. Interestingly, rotamers were encountered for formamides prepared from primary amines or unsymmetrical secondary amines; the ratio of which was determined by comparison of the relative integrals for each species within the ^1H NMR spectra. Although the conditions help minimise imine formation, in some instances small quantities were observed.

The *N*-formylation of primary aliphatic amines with **354** (Table 35, entries 1-7) was particularly facile; typically affording the corresponding formamides in good to excellent yields (81-95%) after just 1 hour. Pleasingly, mildly acid sensitive functionalities, such as furyl and dimethyl acetal groups, were well tolerated and remained unaffected under the developed conditions (Table 35, entry 3 and 7). Furthermore, reaction of **354** with tryptamine (**529**) resulted in exclusive formylation of the primary amine moiety, with competitive formylation of the indole fragment not observed (Table 35, entry 4). Whilst the formamide of sterically congested benzhydrylamine was isolated in a high 83% yield (Table 35, entry 5), the formylation of *tert*-butylamine was less successful; furnishing the *N*-formyl species **542** in only 53% isolated yield (Table 35, entry 6). The slightly reduced yield for the latter may potentially be attributed to competitive imine formation and the volatility of the product. It is noteworthy that this reaction was performed in ethyl acetate, as the mixture became extremely viscous upon addition of the *tert*-butylamine.

Secondary aliphatic amines were also amenable to the developed methodology (Table 35, entries 8-10), with moderate to excellent yields of the isolated *N*-formylated products achieved (56-96%). A superior yield was obtained for secondary cyclic amine 1-phenylpiperazine (entry 10) relative to the acyclic species examined (entries 8 and 9). This is often observed due to the greater basicity and nucleophilicity of a cyclic secondary amine relative to its straight chain, acyclic counterpart, which arises from the reduced steric shielding of the nitrogen lone pair within the former.^{424,534,619} However, in this instance based on the conversion observed within the crude ¹H NMR spectra it appears that the volatility of the acyclic secondary formamides may play a greater role in the slightly reduced isolated yields.

Table 35. *N*-Formylation of a range of amines using formate ester **354**.

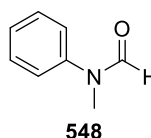
$ \begin{array}{ccc} \begin{array}{c} \text{R}^1 \\ \\ \text{N}-\text{H} \\ \\ \text{R}^2 \end{array} & \xrightarrow[\text{Neat, 1 h}]{\text{Formate ester } \mathbf{354} \text{ (1.5 eq)}} & \begin{array}{c} \text{O} \\ \\ \text{R}^1-\text{N}-\text{C}-\text{H} \\ \\ \text{R}^2 \end{array} \\ \mathbf{524, 527-537} & & \mathbf{525, 538-548} \end{array} $			
Entry	Amine (524, 527-537)	Formamide (525, 538-548)	Yield (%)
1	 524	 525	89
2	 527	 538	82

3	 528	 539	81
4 ^a	 529	 540	90
5	 530	 541	83
6 ^a	 531	 542	53
7	 532	 543	95
8	 533	 544	74
9	 534	 545	56
10	 535	 546	96
11	 536	 547	90

12



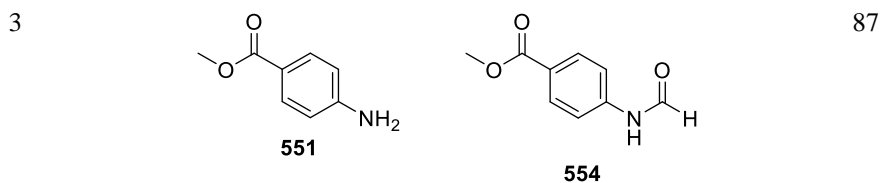
91

^aPerformed in EtOAc.

Whilst alkyl substituents enhance the nucleophilicity of an amino group *via* inductive effects, aryl substituents conversely act to decrease the nucleophilicity, as the lone pair of the nitrogen is conjugated with the aromatic ring.^{496,620} This resonance effect reduces the availability of the lone pair, which in turn lowers the reactivity of the amine towards electrophiles such as formylating reagents.⁶²⁰ Thus, attempts were made to extend the developed methodology to substituted aniline derivatives (Table 35 and Table 36). Pleasingly, both aniline and its secondary *N*-methyl structural analogue generated the desired formamides in excellent yields (90% and 91% respectively) after treatment with **354** for 1 hour (Table 35, entries 11 and 12). Based on the reactivity of formate ester **354** towards these aromatic amines and the reportedly more facile formylation of electron rich anilines,^{496,501,515,563,599} studies were subsequently focussed on less nucleophilic derivatives bearing electron withdrawing substituents. Accordingly, introduction of a halogen or mildly deactivating ester functionality at the *para*-position of the aniline ring was found to retard the rate of formylation with **354** (Table 36). Nevertheless, high to excellent yields (87-95%) were universally achieved after an extended reaction time of 24 hours, without the need for a catalyst or the use of elevated temperatures.

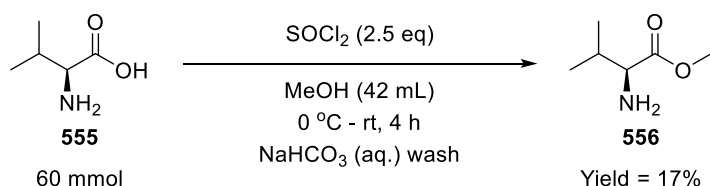
Table 36. *N*-Formylation of mildly deactivated anilines with formate ester **354**.

Entry	Amine (549-551)	Formamide (552-554)	Yield (%)
1	<p style="text-align: center;">549</p>	<p style="text-align: center;">552</p>	95
2	<p style="text-align: center;">550</p>	<p style="text-align: center;">553</p>	94



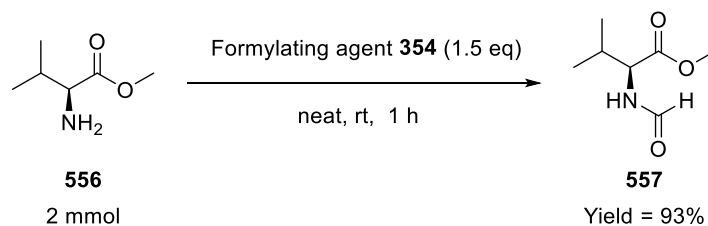
3.3.3 *N*-Formylation of a carboxyl protected amino acid

As previously detailed, *N*-formyl amino acid derivatives have been applied within the synthesis of peptides in order to prevent undesired polymerisation and side chain reactions occurring.⁵¹⁷⁻⁵²⁰ To determine the viability of **354** as a formyl donor for the preparation of such synthetically relevant precursors, the formylation of carboxyl-protected amino acid ester **556** was examined. L-Valine methyl ester was first prepared from the esterification of the parent amino acid using thionyl chloride acidified methanol (Scheme 283).⁶²¹ Thionyl chloride was added dropwise to a stirring suspension of L-valine in methanol at 0 °C and after stirring at room temperature for 4 hours, the reaction mixture was concentrated *in vacuo*.⁶²¹ The crude residue was dissolved in ethyl acetate and washed with saturated aqueous sodium bicarbonate solution to afford the free base of L-valine methyl ester in analytically pure form.



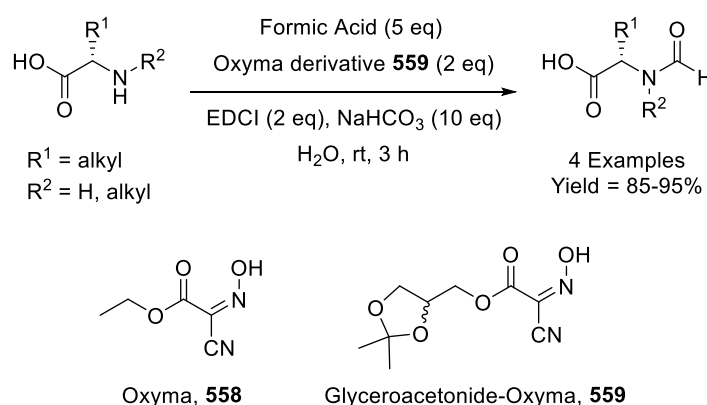
Scheme 283. Esterification of L-valine (**555**) using thionyl chloride acidified methanol to afford L-valine methyl ester (**556**).⁶²¹

Enantiomerically pure *N*-formyl amino acid derivative **557** was then synthesized in excellent yield (93%), with full retention of the methyl ester functionality, by simply mixing L-valine methyl ester with formate ester **354** for 1 hour (Scheme 284). Racemisation of the stereogenic centre was not observed, as determined by comparison of the specific rotation value with those reported in the literature: measured $[\alpha]_D^{20} = -22$ ($c = 1.0$, EtOH); reported $[\alpha]_D^{20} = -23.73$ ($c = 2.0$, EtOH).⁵⁷³ Thus, **354** is an effective *N*-formylating reagent for amino acid esters as well as structurally diverse amines of varying nucleophilicity.

Scheme 284. *N*-Formylation of L-valine methyl ester (**556**) with formate ester **354**.

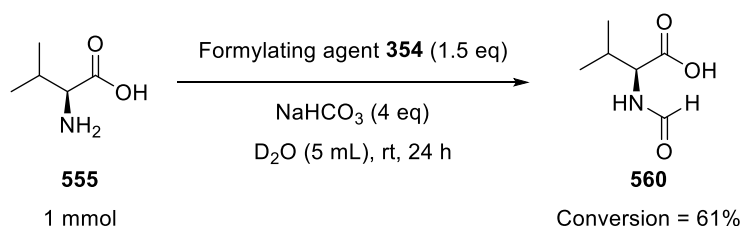
3.3.4 *N*-Formylation of an unprotected amino acid

Although several formylating reagents have been reported for the *N*-formylation of carboxyl protected amino acid derivatives, extension of these methods to unprotected analogues has not been achieved. It is due to the instability of many formylating reagents in aqueous medium and the poor solubility of amino acids in organic solvents, that direct formylation of unprotected amino acids remains a particular challenge. A notable exception to this was published in 2013 by Kurosu and co-workers (Scheme 285).⁶¹⁸ The authors reported that ethyl 2-cyano-2-(hydroxyimino)acetate (Oxyma) derivative **559** could successfully be used in water to selectively install an *N*-formyl group onto α -amino acids, among other amino substrates, in high yield (85-95%).⁶¹⁸ Despite the effectiveness of this approach, the method suffers from an extremely high resource demand and associated waste, as a five equivalent excess of formic acid, a coupling reagent (EDCI, 2 equiv.), base (NaHCO₃, 10 equiv.) and two equivalents of the Oxyma derivative **559** are all required to promote the desired transformation.⁶¹⁸ Oxyma (**558**) itself could be employed using a 9:1 DMF:H₂O mixture, however significantly reduced yields were attained (30-60%).⁶¹⁸ Interestingly, formylations with triethyl orthoformate have been successfully conducted in water, however this reagent has not been applied to unprotected amino acids.^{531,540}

Scheme 285. *N*-Formylation of unprotected amino acids using glyceracetone-Oxyma **559**.⁶¹⁸

Based on the relative water stability of **354**, its ability to function as a formylating reagent in the presence of water (Table 33, entry 1) and the fundamental importance of the transformation described, attempts were made to apply the developed methodology to unprotected amino acids. Specifically, formate ester **354** was added in a single portion to a stirring solution of L-valine

(**555**) and sodium bicarbonate in deuterated water (Scheme 286). The resulting mixture was stirred at room temperature for 24 hours, before an aliquot was removed for analysis by ^1H NMR spectroscopy. By comparison of the relative integral for the starting material peak at 3.61 ppm with those for the formamide rotamers at 3.79 and 4.14 ppm, it was determined that 61% conversion of L-valine into the *N*-formyl protected species (**560**) had been achieved. Attempts to enhance the conversion further by increasing the amount of formylating reagent (2.5 equiv.) and employing a mixed solvent system (0.5:4 mL of THF:D₂O) to promote homogeneity did not lead to superior results. Although further optimisation is still required, the results from this preliminary study are extremely promising and suggest that the use of **354** alone may provide a simple and less wasteful protocol for accessing *N*-formyl amino acids.

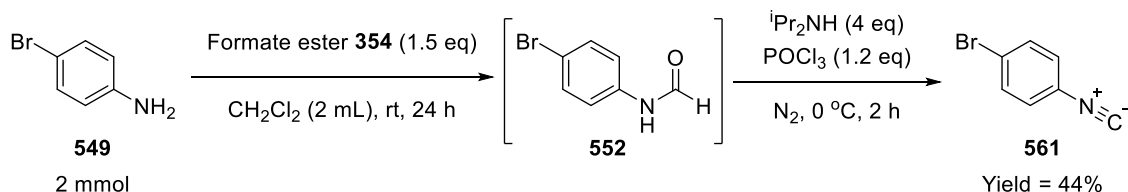


Scheme 286. *N*-Formylation of unprotected L-valine (**555**) with formate ester **354** in D₂O.

3.3.5 Developing a one pot synthesis of isocyanides from amines

As highlighted previously within this chapter, formamides are a direct precursor to isocyanides.^{504,505} Due to the current interest in isocyanides from both a biological and synthetic perspective,^{506,507,622} attempts were made to develop a one-pot procedure for the direct synthesis of isocyanides from amines *via* an intermediate formamide; formed using **354** as the formylating reagent. Literature precedent exists for the high yielding synthesis of 1-bromo-4-isocyanobenzene (**561**) from isolated *N*-(4-bromophenyl)formamide (**552**) using phosphorus(V) oxychloride, POCl₃, as the dehydrating reagent in DCM.⁶²³ Therefore, it was considered that these conditions may be viably adapted for use in conjunction with the developed formylation methodology.^{623,624} Initially, *N*-(4-bromophenyl)formamide (**552**) was generated *in situ* by stirring a dichloromethane solution of 4-bromoaniline (**549**) and formate ester **354** (1.5 equiv.) at room temperature for 24 hours (Scheme 287). To achieve the subsequent dehydration, the mixture was placed under a nitrogen atmosphere and treated with diisopropylamine (*i*Pr₂NH), before phosphorus(V) oxychloride (POCl₃) was added dropwise at 0 °C and the reaction stirred at this temperature for 2 hours. The reaction was then quenched with saturated aqueous sodium carbonate solution and left to warm to room temperature overnight. Upon extraction and purification by a short silica gel flash column, 1-bromo-4-isocyanobenzene (**561**) was isolated in 44% yield as a characteristically foul smelling yellow solid.⁶²³ Thus, the developed formylation method appears to be compatible to a certain extent with existing dehydration methodology, allowing for its use in the one-pot

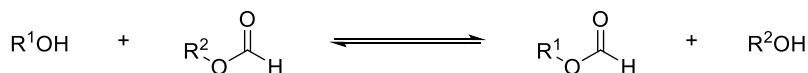
synthesis of isocyanides from amines. However, a larger excess of diisopropylamine was required to account for the acetic acid generated as a by-product within the first step. Further improvement to the yield may be possible by employing an alternative dehydrating reagent or modification of the reaction conditions and it is of interest to examine the generality of this methodology.



Scheme 287. Applying the developed methodology to the one pot synthesis of 1-bromo-4-isocyanobenzene (**561**) from 4-bromoaniline (**549**).^{623,624}

3.3.6 *O*-Formylation of primary alcohols

The analogous *O*-formylation of alcohols to generate formate esters is of equal synthetic value; allowing for the protection of alcohols⁶²⁵ and providing access to industrially relevant compounds. For instance simple formate esters have found application as ingredients within fragrances due to their pleasing odour.⁶²⁶⁻⁶²⁸ However, this transformation is typically more difficult to achieve due to the reduced nucleophilicity of alcohols relative to the structurally equivalent amines.^{515,555,558,629} Additionally, in instances where an alcohol is generated as a by-product, the reversibility of the reaction is a further consideration, as an equilibrium will be established between the formate ester reagent and formate ester product (Scheme 288).⁵⁰¹ However, the use of **354** should overcome the latter problem, as previously described.

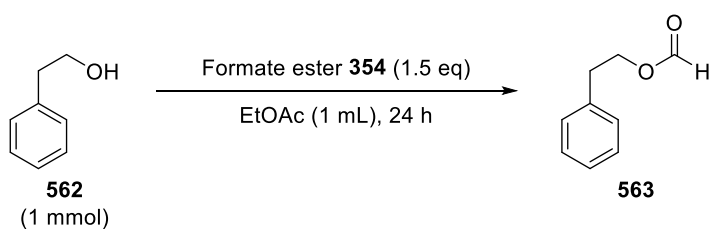


Scheme 288. Equilibrium established for the *O*-formylation of alcohols using formate esters that generate an alcohol by-product.

As anticipated the neat formylation of primary alcohol **562** with **354** was relatively sluggish at room temperature, with only 15% conversion into formate ester **563** observed after 24 hours (Table 37, entry 1). Pleasingly, by performing the reaction at $40\text{ }^\circ\text{C}$ a significant improvement in reaction rate could be achieved (Table 37, entry 2). Bases such as imidazole have been reported to aid the formylation of alcohols by enhancing the nucleophilicity of the hydroxyl group through removal of the proton.⁶¹¹ However, following the success of other weak bases, such as sodium bicarbonate, acetates and benzoates in promoting the addition of a peracid nucleophile to a carbonyl group within the Baeyer-Villiger oxidation (Chapter 2), it was of interest to determine whether a similar strategy could be employed to activate the alcohol nucleophile. It was reasoned that sodium bicarbonate may function as a general base within the *O*-formylation.

Repeating the reactions in the presence of two equivalents of sodium bicarbonate as a slurry in ethyl acetate gave slightly reduced conversion relative to the solvent and base free protocols at each temperature (Table 37, entries 3 and 4). Intriguingly, conducting the formylation neat and in the presence of solid base alone gave greatly improved results (Table 37, entries 5 and 6); indicating that solvent inhibits the *O*-formylation reaction. The effect of the base was particularly apparent for the room temperature reaction, with 72% conversion achieved relative to 15% in the absence of the basic additive within the neat systems (Table 37, entries 1 and 5).

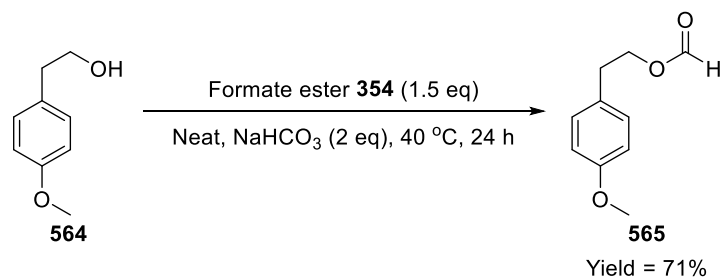
Table 37. Optimisation of the reaction conditions for the *O*-formylation of 2-phenylethanol (562**) with formate ester **354**.**



Entry	Solvent	Base (2.0 equiv.)	Temperature (°C)	Conversion into 563 ^a
1	Neat	No base	rt	15
2	Neat	No base	40	63
3	EtOAc	NaHCO ₃	rt	6
4	EtOAc	NaHCO ₃	40	60
5	Neat	NaHCO ₃	rt	72
6	Neat	NaHCO ₃	40	91

^aProduct ratios were determined by ¹H NMR spectroscopic analysis.

Unfortunately, attempts to isolate formate ester **563** by column chromatography were unsuccessful, due to co-elution of the benzaldehyde by-product. Therefore, the developed methodology was applied to the structurally related but more polar alcohol **564** and pleasingly after work-up and purification formate ester **565** was isolated in 71% yield (Scheme 289). Subsequent work within the group has examined the substrate scope for this *O*-formylation reaction using **354**, with a diverse range of alcohols amenable to the developed methodology. The method has also been successfully extended to the protection of phenols; albeit employing more forcing conditions.



Scheme 289. *O*-Formylation of 4-methoxyphenethyl alcohol (**564**) with formate ester **354** using the optimised conditions.

It is proposed that the sodium bicarbonate may be functioning as a general base to facilitate proton transfer from the alcohol nucleophile in the rate determining step or alternatively it may generate sodium acetate from the acetic acid by-product, which may function in an analogous manner. If indeed this is the mode of activation, it may be anticipated that *N*-oxides, which are exceptional hydrogen bond acceptors, may also facilitate the reaction. Additionally, it may be possible to employ catalytic amounts of the general base. As a result of the disparity in reactivity observed between alcohols and amines, it may be anticipated that formate ester **354** can be employed as a chemoselective formylating reagent; allowing for selective *N*-formylation of amines in the presence of unprotected alcohols.^{555,556} However, these areas of investigation were beyond the scope of this work. Additionally, it is proposed that implementing a lower molecular weight formate ester derivative (**566**) may allow for a volatile aldehyde to be generated upon fragmentation; greatly simplifying the isolation method (Figure 66).

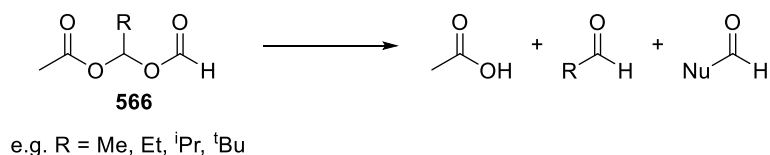


Figure 66. Potential formate ester analogues that produce a volatile aldehyde by-product.

3.4 Conclusion

A solvent and catalyst free protocol for the direct formylation of amino functionality using novel formate ester **354** at room temperature has been developed. For solid substrates or where the reaction solidified an ethyl acetate solution was employed. Formate ester **354** is an effective formylating reagent for the high yielding *N*-formylation of primary and secondary (aliphatic and aromatic) amines as well as amino acid esters; tolerating a wide range of functional groups. Due to the relatively high reactivity of **354**, a short reaction time of 1 hour could be employed for all substrates except mildly deactivated anilines. For these typically sluggish species, the formyl group was instead successfully installed over an extended 24 hour period. Demonstrating its synthetic utility, the developed methodology was found to be compatible with POCl₃ dehydration conditions, allowing for the one-pot synthesis of 1-bromo-4-isocyanobenzene from 4-bromoaniline. Formate ester **354**, which may be prepared from commercially available (*E*)-4-phenyl-3-buten-2-one *via* a one-step operationally simple procedure, is relatively bench stable and compatible with aqueous conditions. As such, promising results have been achieved for the selective *N*-formylation of the unprotected amino acid L-valine in water. Additionally, formate ester **354** has been successfully applied to the *O*-formylation of primary alcohols, allowing access to the corresponding formate esters. In this instance the neat reaction is performed at 40 °C in the presence of sodium bicarbonate as a general base.

4 *N*-Oxides as organocatalysts for electrophilic aromatic brominations

4.1 Introduction

Whilst *N*-oxides have found application as organocatalysts, their use has been largely limited to silicon chemistry. Therefore, it was of interest to examine the utility of *N*-oxides as nucleophilic catalysts beyond this particular application, with the aim of extending the range of reactions in which they might be employed. Electrophilic aromatic bromination was identified as a fundamental organic reaction that could be conducive to nucleophilic catalysis by *N*-oxides.

4.1.1 Electrophilic aromatic brominations

Brominated arenes and heterocycles are an important class of compound that feature heavily within natural products; particularly those derived from marine origins (**567-569**, Figure 67).⁶³⁰⁻⁶³⁶ Such aryl bromides have been found to possess interesting biological properties including antifungal, antibacterial, antineoplastic, antiviral and anti-inflammatory activity.⁶³⁰⁻⁶³⁴ Ring brominated aromatics are also important components of flame retardants, fuel additives, pharmaceuticals and agrochemicals, with incorporation of the bromine functionality often affording the desired properties.^{630,637-641}

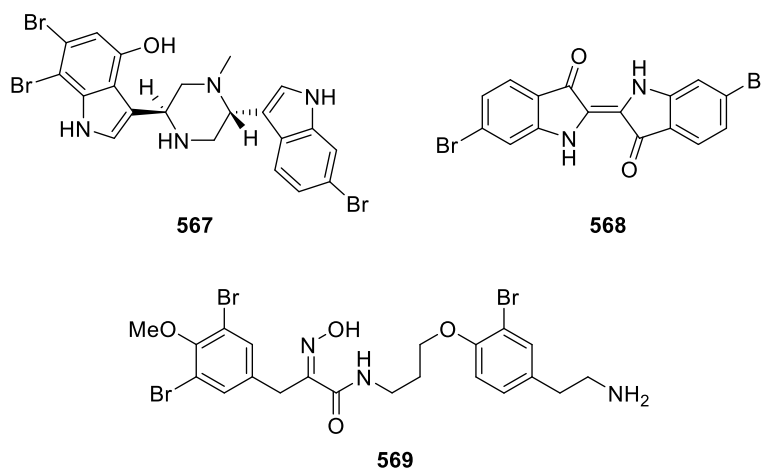
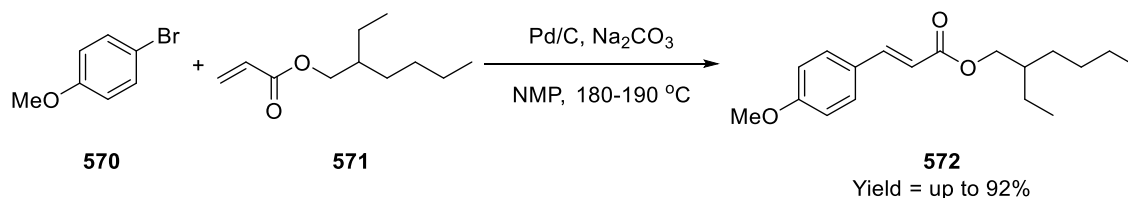


Figure 67. Examples of biologically active natural products containing an aryl bromide functionality.^{632,634}

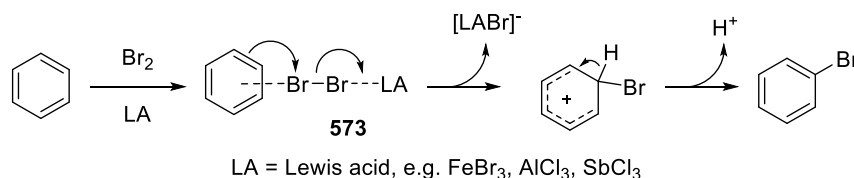
As well as being important synthetic targets, aryl bromides are also highly versatile building blocks.⁶⁴² Among other applications, aryl bromides 1) undergo transition metal catalysed cross-coupling reactions to form new C-C, C-N, C-O and C-S bonds,⁶⁴³⁻⁶⁴⁵ 2) are precursors to organometallic compounds such as organolithium and Grignard reagents,^{646,647} 3) may be reactive towards nucleophilic aromatic substitution reactions⁶⁴⁸ and 4) can be converted into aryl radicals.^{70,636,637,642,649-652} Therefore, bromoarenes are frequently employed as key synthetic

intermediates in the manufacture of pharmaceuticals, agrochemicals and other speciality chemicals.^{638,649,653,654} For instance, UV-B sunscreen agent **572** is prepared on tonne scale from the Pd/C catalysed Heck reaction of *p*-bromoanisole (**570**) and 2-ethylhexyl acrylate (**571**) (Scheme 290).⁶⁵⁵



Scheme 290. Preparation of UV-B sunscreen agent **572** from *p*-bromoanisole (**570**).⁶⁵⁵

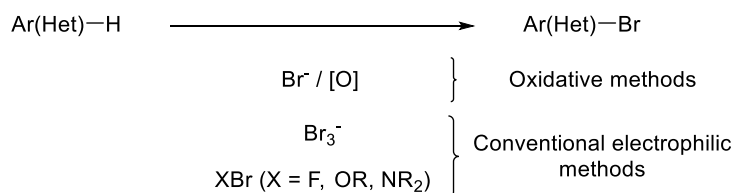
Aryl bromides are most commonly accessed *via* electrophilic aromatic substitution reactions, which is traditionally performed with elemental bromine in a chlorinated solvent or acidic medium (Scheme 291).^{650,656-660} Whilst the bromination of electron rich substrates may occur readily, unactivated aromatics require the presence of a strong Lewis acid catalyst, such as FeBr₃, AlCl₃ or SbCl₃.^{630,637,659,661,662} Complexation of Br₂ to the Lewis acid to form adduct **573** enhances the electrophilicity of the molecular bromine *via* polarisation of the Br-Br bond, which facilitates the substitution reaction (Scheme 291).⁶³⁷ Within these systems, the electronics of the aromatic also dictate the position at which substitution will occur and therefore the substitution patterns accessible.^{630,650,662} In addition to these electronic restraints, there are several problems inherent to bromination reactions. For instance, reactions with elemental bromine may be exothermic and unselective, with polybromination, mixtures of regioisomeric products and radical induced benzylic and side chain bromination sometimes observed.^{630,636,650,656,663} Furthermore, the Lewis acids required are often corrosive and moisture sensitive; generating stoichiometric quantities of HX (X = Br, Cl etc) upon aqueous work-up.^{649,660,661,664} As a result of these issues, bromination reactions are often subject to separation difficulties and reduced yields, which can prove problematic particularly on scale.^{650,661,665}



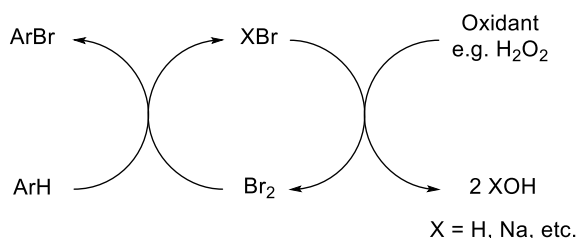
Scheme 291. Mechanism of Lewis acid catalysed electrophilic aromatic bromination.⁶⁶⁶

Throughout the past few decades much research has been focussed on developing alternative brominating agents to avoid the use of molecular bromine.^{657,667} Specifically, these strategies entail *in situ* generation of bromine from an inorganic bromide source under oxidative conditions (i.e. in the presence of: hydrogen peroxide, oxygen, sodium perborate, lead tetraacetate,

cerium(IV) ammonium nitrate, Oxone[®] (2KHSO₅•KHSO₄•K₂SO₄), (diacetoxyiodo)benzene or sodium periodate) or the use of reagents involving bromine bound to an electronegative atom, such as Br, F, N or O (Scheme 292 and Scheme 293).^{630,657,664,668} This latter class of reagent encompasses bromo-organic compounds as well as ionic tribromides and the use of solid supported bromine as ‘bromine carrying agents.’^{630,657,667-669}



Scheme 292. Alternative brominating strategies that avoid the direct use of molecular bromine.⁶³⁰



Scheme 293. Oxidative bromination catalytic cycle.^{668,670}

To date, over 100 organic brominating agents have been reported for use in bromination reactions as well as other transformations.⁶⁶⁷ However, it should be noted that a catalyst may still be required for these reagents to be effective.^{663,671} Interestingly, many of the organic brominating reagents feature an N-Br bond, including: *N*-bromosuccinimide (NBS) (**574**),⁶⁷² *N*-bromoacetamide (**575**),^{673,674} *N,N*-dibromophenylsulfonamide (**576**)^{674,675} and *N*-bromo-*tert*-butylamine (**577**),⁶⁷⁶ which have been applied as alternative electrophilic brominating agents for the ring bromination of aromatics (Figure 68).^{630,667,677} However, of particular relevance to this work is the use of freshly prepared dioxane dibromide (**578**), in which the oxygen coordinates to the bromine, for the bromination of activated aromatics.^{656,678} For instance, Bhar *et al.* reported that this bromine complex can be used to achieve highly regioselective electrophilic aromatic brominations under solvent free conditions; affording monobrominated products in high yield (Scheme 294).⁶⁵⁶

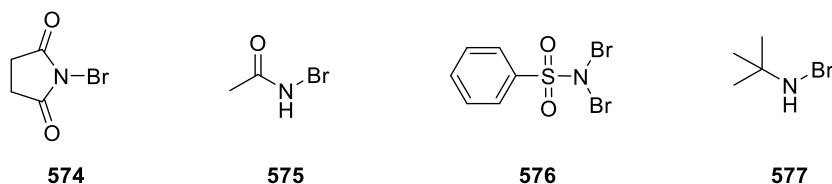
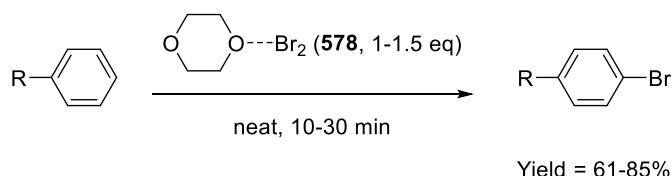


Figure 68. Common organic brominating agents containing an N-Br bond.⁶⁷²⁻⁶⁷⁶

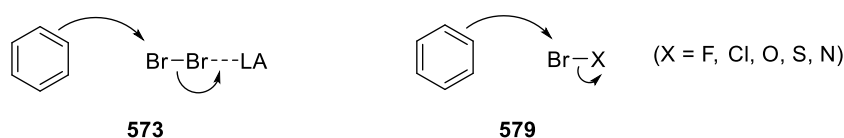


Scheme 294. Application of dioxane dibromide as a brominating agent for electron rich aromatics.⁶⁵⁶

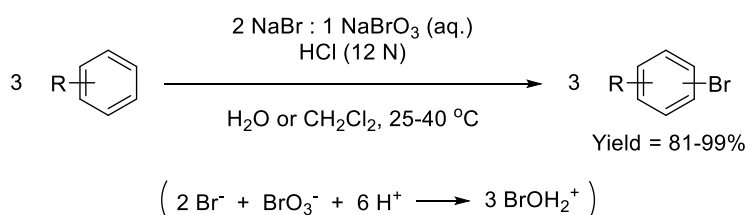
Nevertheless, many of these alternative brominating reagents are prepared using molecular bromine; ultimately transferring its use to an earlier synthetic step.^{636,638,657} Additionally, in some instances these reagents may not be stable or readily available.^{663,679} The technological requirements are not simplified by the *in situ* generation of bromine relative to the use of molecular bromine directly; for which equipment and procedures are already well established.^{657,680} Furthermore, when employing a bromine generating species the yield may be highly influenced by the concentration of the reagent and reaction temperature.⁶⁵⁹ Both conventional bromine containing reagents and oxidative processes suffer from high resource demand and waste relative to the traditional procedure involving molecular bromine alone.^{657,659} However, in some instances there is the potential to recycle the bromine carrying agent, albeit with a higher associated solvent consumption.^{636,657} Although molecular bromine is a toxic, corrosive and difficult to handle liquid, it is one of the most cost effective and atom efficient brominating agents as well as being readily available and versatile.^{636,657,667,681} Consequently, molecular bromine is still frequently employed in both industry and academia.^{638,681}

Molecular bromine may be activated *via* polarisation of the Br-Br bond, which enhances the electrophilicity of this reagent and therefore makes it more susceptible to nucleophilic attack by the π -system of the aromatic.⁶³⁷ This may be achieved *via* coordination of the bromine to a hard Lewis acid centre (**573**), as previously detailed, or alternatively through homogeneous catalysis involving the formation of a polar Br-X bond (**579**), for which X is a more electronegative atom such as: F, Cl, O, S or N (Scheme 295).⁶³⁷ For the latter strategy, Br-X is typically generated *in situ* and due to the bond polarisation it functions as a source of electropositive bromine, with X acting as a nucleofuge.⁶³⁷ For instance, in the ambient temperature bromination of aromatics reported by Ranu, Ghosh and co-workers, BrOH_2^+ is proposed to be formed as the reactive

brominating species *in situ* via acidification of the 2:1 sodium bromide:sodium bromate reagent with 12 N hydrochloric acid (Scheme 296).⁶⁸² Interestingly, BrOH_2^+ was found to be more reactive than molecular bromine.⁶⁸² Adimurthy *et al.* subsequently demonstrated that this methodology could be applied to other heterocycles using sulfuric acid to generate the reactive brominating species.⁶⁸³ The same reactive bromine species is proposed to form during the α -bromination of ketones with ammonium bromide and Oxone[®].⁶⁸⁰ Similarly, oxoacids (AOH) are thought to react with bromine to provide an electrophilically activated species (BrOA); the brominating ability of which increases with enhanced stability of the leaving group (AO^-).⁶³⁷ Owing to the success of species containing a Br-O bond, we were interested in determining whether *N*-oxides could act in a similar manner *via* formation of a complex with bromine. This type of activated adduct would contain a highly stable *N*-oxide nucleofuge, which based on previous findings might be anticipated to promote facile bromination.



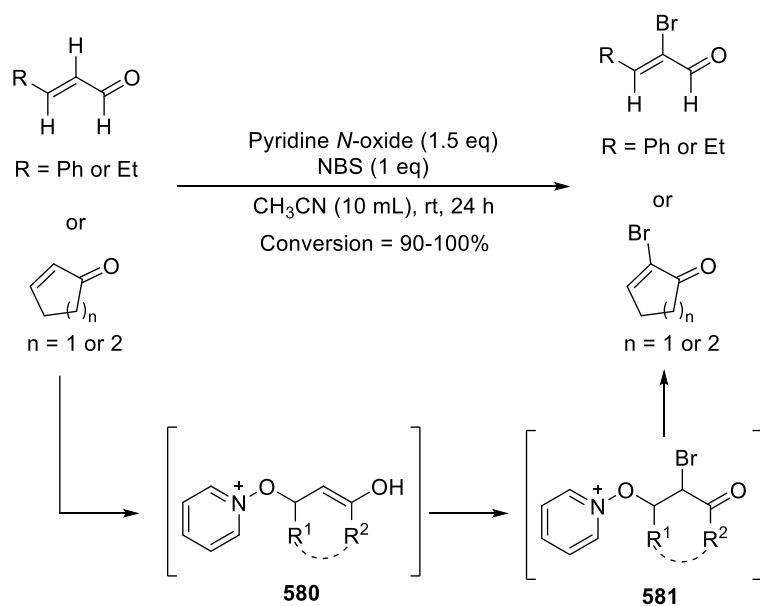
Scheme 295. Methods for enhancing the electrophilicity of elemental bromine.⁶³⁷



Scheme 296. *In situ* generation of BrOH_2^+ as an active brominating agent.⁶⁸²

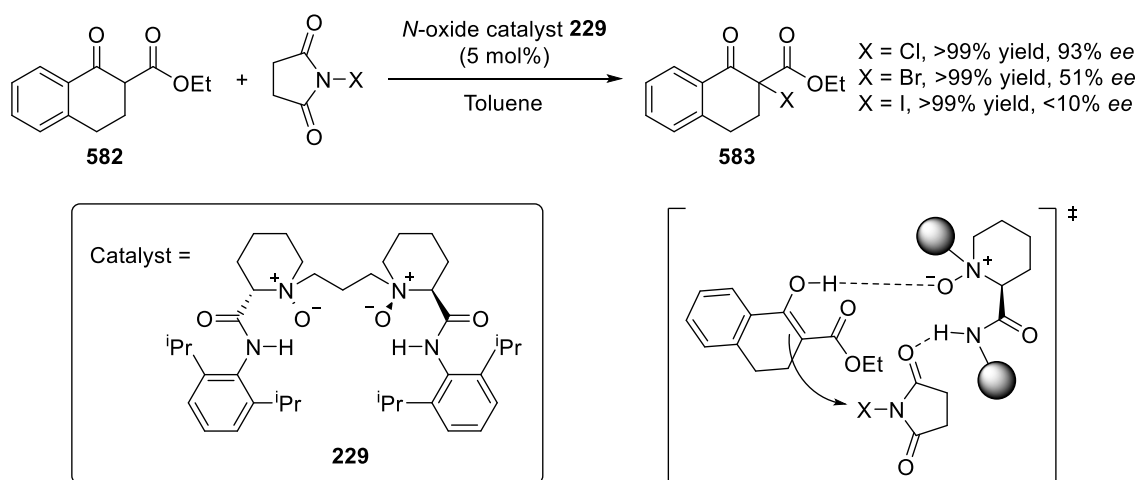
4.1.2 *N*-Oxides as catalysts within bromination reactions

To the best of our knowledge, the work recently published by Bovonsombat and co-workers, concerning the α -bromination of cyclic enones and linear enals, represents the first reported example of *N*-oxide promoted brominations (Scheme 297).²¹⁵ Specifically, the reactions were performed using NBS as the bromine source and stoichiometric quantities (1.5 equiv.) of pyridine *N*-oxide were required.²¹⁵ However, in this instance the authors have proposed that the reaction proceeds *via* intermediate **580**, with the *N*-oxide undergoing conjugate addition to the α,β -unsaturated substrate rather than generating an *N*-oxide bromine complex (see section 1.4.7).²¹⁵ The resulting enol is then brominated to afford a new intermediate **581** that then undergoes *syn*-elimination of the α -hydrogen and *N*-oxide species to afford the corresponding α -brominated products with retention of the double bond stereochemistry.²¹⁵



Scheme 297. Pyridine *N*-oxide promoted α -bromination of linear enals and cyclic enones.²¹⁵

As highlighted in Chapter 1, bifunctional *N,N'*-dioxide **229** has been successfully adopted as an organocatalyst for the asymmetric α -chlorination of cyclic β -ketoesters with NCS (Scheme 298).²¹⁸ The *N*-oxide moiety is again responsible for activating the substrate towards halogenation, albeit *via* favourable hydrogen bonding interactions in this instance.^{2,218} Furthermore, the electrophilicity of the NCS is simultaneously enhanced *via* hydrogen bond donation from the NH of the amide functionality of **229**.^{2,218} Notably, preliminary studies focussed on extending this methodology to the analogous α -bromination with NBS were met with reasonable success.²¹⁸ More specifically, the *N*-oxide catalysed bromination of β -ketoester **582** afforded the desired product **583** in almost quantitative yield but with considerably reduced enantioselectivity relative to the analogous chlorination (*cf.* 51% *vs* 93% *ee*).²¹⁸



Scheme 298. *N,N'*-Dioxide **229** as a bifunctional catalyst for the α -halogenation of β -ketoester **582**.^{2,218}

Nevertheless, literature precedent exists for the formation of complexes between aromatic *N*-oxides (pyridine, quinoline and acridine) and bromine, which is a σ -type acceptor, in both 1:1 and 2:1 stoichiometries (Figure 69).⁶⁸⁴⁻⁶⁸⁶ Andreev *et al.* have reported that, within the IR spectrum of the acridine *N*-oxide complex, a reduction in the intensity of the absorption band assigned to the dative N \rightarrow O bond can be attributed to complexation of bromine to the oxygen of the *N*-oxide.⁶⁸⁴⁻⁶⁸⁶ This type of interaction is commonly observed for hard Lewis acids, whilst soft Lewis acids, such as iodine, coordinate primarily to the π -system of the aromatic ring.⁶⁸⁴ Despite their lower basicity, *N*-oxides have been reported to form more stable complexes with σ -type acceptors relative to the corresponding amine, which has been rationalised in terms of the accessibility of the oxygen donor atom and the polarisation of the N \rightarrow O bond.^{687,688} Bromine based complexes can simply be prepared by addition of elemental bromine to a chloroform solution of the *N*-oxide species.⁶⁸⁴ Whilst the composition and stoichiometry of these complexes have been determined using various analytical techniques, including gravimetric analysis, their exact structure remains unclear.⁶⁸⁴⁻⁶⁸⁶ However, several bridged structures have been proposed, as shown in Figure 69.⁶⁸⁴⁻⁶⁸⁶

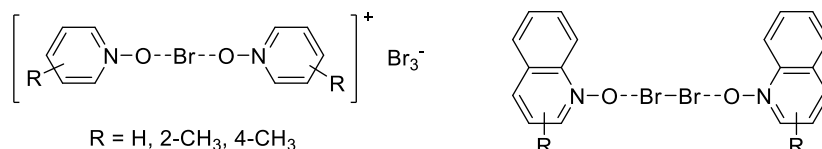
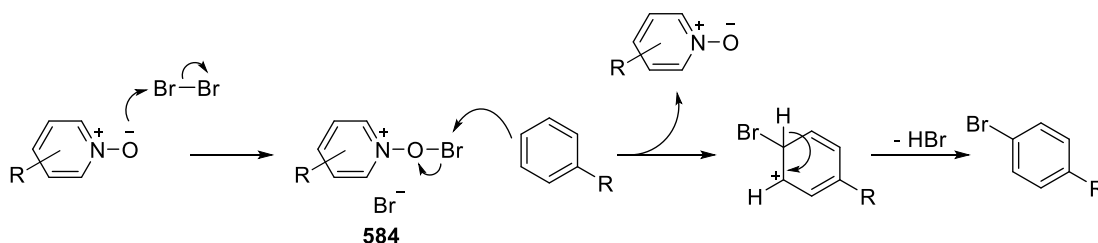


Figure 69. Proposed structures for aromatic *N*-oxide bromine complexes.^{685,686}

4.2 Project Aims

Although *N*-oxide bromine complexes have been prepared, their potential to act as a reactive source of electrophilic bromine has not yet been investigated and this application therefore formed the basis of this work. As these complexes are known to form under standard bromination conditions, we were specifically interested in developing a methodology that utilised catalytic quantities of the *N*-oxide. The reactive species, which is shown for simplicity as **584**, would be formed and regenerated *in situ* (Scheme 299). Consequently, this catalytic regeneration strategy would remove the need to preform stoichiometric quantities of the activated brominating agent; reducing the associated resource demand and waste. Not only would this provide a simple organocatalytic protocol for electrophilic aromatic brominations but would also allow for the potential of *N*-oxides as nucleophilic catalysts to be further examined; an area of chemistry that remains to be fully explored.

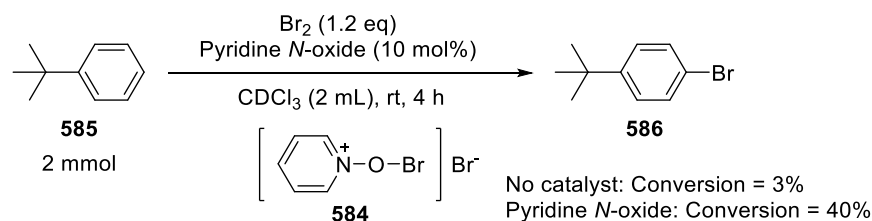


Scheme 299. Potential electrophilic activation of elemental bromine *via* formation of an *N*-oxide bromine complex.

4.3 Results and Discussion

4.3.1 Development of *N*-oxide catalysed methodology

Initial work was focussed on determining the ability of pyridine *N*-oxide to catalyse the room temperature bromination of *tert*-butylbenzene (**585**) with elemental bromine in chloroform (Scheme 300); conditions that have been reported to promote complex formation.⁶⁸⁴ *tert*-Butylbenzene was selected as the model substrate, as it was anticipated that the electron donating nature and steric bulk of the *tert*-butyl group should ensure that a single monobrominated product with *para*-substitution was afforded; thus simplifying analysis. Additionally, the electron releasing inductive effect of this alkyl substituent should mildly activate the aromatic ring towards electrophilic aromatic substitution. To simplify the procedure and improve conversion data accuracy, the reactions were performed in deuterated chloroform (CDCl₃) wherever possible; allowing for the ¹H NMR spectra to be obtained directly for the crude reaction mixture.



Scheme 300. Examining the catalytic potential of pyridine *N*-oxide within the bromination of *tert*-butylbenzene (585**).**

As anticipated, reactions performed both in the presence and absence of pyridine *N*-oxide afforded a single regioisomeric product with *para*-substitution, as determined by the upfield shift of the *tert*-butyl resonance and the coupling pattern of the aromatic peaks within the ¹H NMR spectra (Figure 70). Pleasingly, the reaction conducted in the presence of 10 mol% pyridine *N*-oxide proceeded to 40% conversion, whilst the background reaction was found to achieve only 3% conversion into **586** after 4 hours; as determined by comparison of the relative integrals of the *tert*-butyl resonances at δ 1.37 ppm for **585** and δ 1.34 ppm for **586** (Figure 70).⁶⁸⁹ Therefore, the *N*-oxide appeared to be functioning as a catalyst within the reaction.

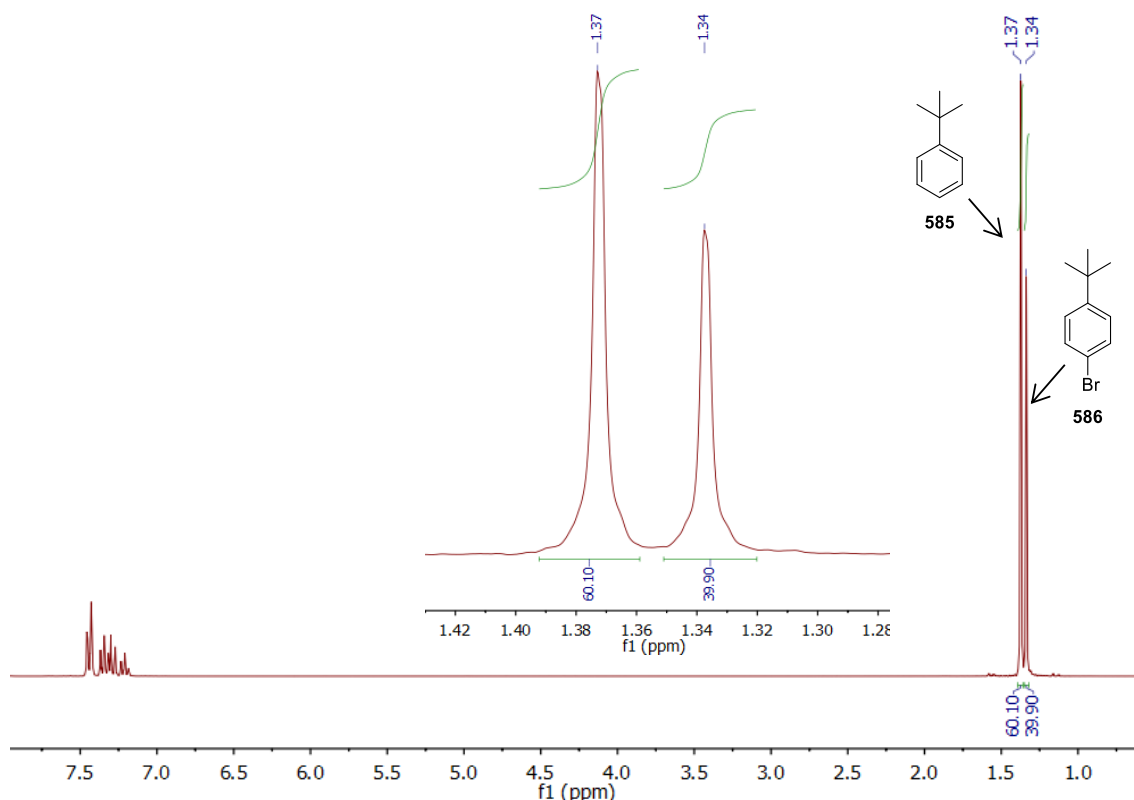


Figure 70. 300 MHz ¹H NMR spectrum obtained in CDCl₃ for the pyridine *N*-oxide catalysed bromination of *tert*-butylbenzene (585) with elemental bromine.

A range of organocatalysts, encompassing sp³ hybridised *N*-oxides, sp² hybridised *N*-oxides, amines and phosphines, were then screened to assess their potential as catalysts within the aforementioned bromination reaction (Table 38). Both aliphatic acyclic and cyclic *N*-oxides (trimethylamine *N*-oxide and *N*-methyl morpholine *N*-oxide respectively) were found to promote the bromination reaction, with trimethylamine *N*-oxide achieving the slightly higher conversion of 41% (Table 38, entries 2 and 3). Next, the electronic demand of heteroaromatic *N*-oxides was investigated by comparing various 4-substituted pyridine *N*-oxide derivatives (Table 38, entries 4-7). Unsurprisingly, 4-nitropyridine *N*-oxide was found to be the least active catalyst (12% conversion), affording only a small increase in conversion over the uncatalysed system (Table 38, entries 1 and 4). The particularly low catalytic activity observed in this instance may be attributed to the increased contribution of resonance forms **E-G** to the resonance hybrid, as a result of the strongly electron withdrawing nature of the nitro group (Figure 71).^{3,418} Specifically, the oxygen of the *N*-oxide would exhibit a lower charge density and therefore formation of an adduct with the bromine would be less favourable. The opposite should hold true for electron rich *N*-oxides, where the alternate resonance forms (**A-D**) would be expected to have an increased contribution (Figure 71).⁴¹⁸

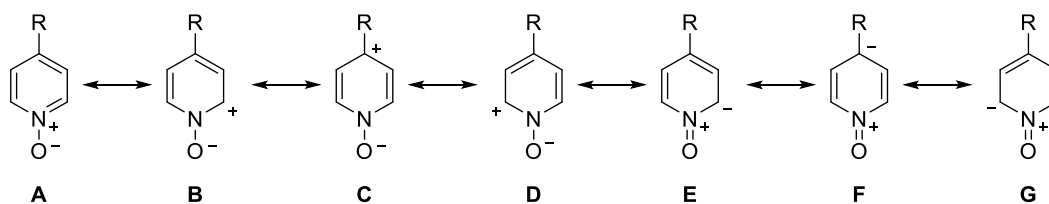
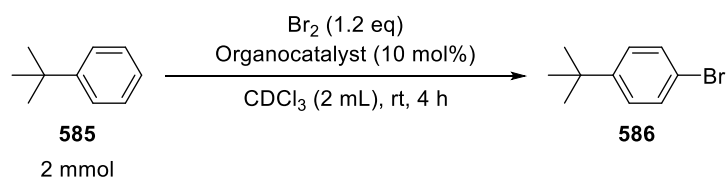


Figure 71. Resonance forms of 4-substituted pyridine *N*-oxide.³

In accordance with this hypothesis, pyridine *N*-oxide and its electron rich derivatives (Table 38, entries 5-7) displayed significantly higher catalytic activity for the bromination reaction than 4-nitropyridine *N*-oxide, with 4-picoline *N*-oxide achieving the highest conversion into **586** (49%) of any catalyst studied. The lower conversion observed for the more electron rich 4-dimethylaminopyridine *N*-oxide relative to pyridine and 4-picoline *N*-oxide was unexpected based on the electronic argument outlined above (Table 38, entry 7). However, the more electron rich 4-dimethylaminopyridine *N*-oxide has been reported to undergo aromatic bromination itself to give the 3-bromo derivative, which would be expected to exhibit lower catalytic activity based on the associated reduction in electron density.⁶⁹⁰ Owing to the success of 4-picoline *N*-oxide, the 2- and 3-substituted regioisomers were examined, which gave comparable but slightly inferior conversions (Table 38, entries 8 and 9). Additionally, 2- and 3-picoline *N*-oxide are highly hygroscopic, making these catalysts difficult to handle and weigh out accurately. The application of fused heterocyclic quinoline *N*-oxide, which has been previously reported to form a 2:1 complex with bromine, was ineffective at further enhancing the extent of reaction (Table 38, entry 10).⁶⁸⁵ Interestingly, amine and phosphine based species were also found to be promising catalysts for the bromination reaction, albeit with slightly reduced catalytic activity relative to the most effective *N*-oxides (Table 38, entries 11-14).

Table 38. Screen of organocatalysts for the bromination of *tert*-butylbenzene (**585**) with bromine.

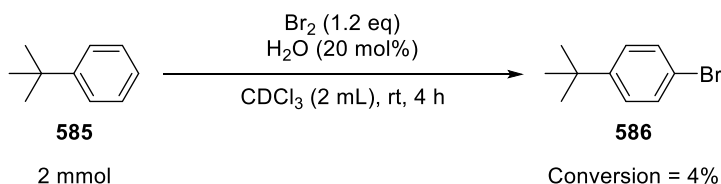


Entry	Identity of Organocatalyst	Conversion (%) ^a
1	No catalyst	4
2	Trimethylamine <i>N</i> -oxide	41
3	<i>N</i> -Methylmorpholine <i>N</i> -oxide	31
4	4-Nitropyridine <i>N</i> -oxide	12
5	Pyridine <i>N</i> -oxide	42
6	4-Picoline <i>N</i> -oxide	49

7	4-Dimethylaminopyridine	34
	<i>N</i> -oxide	
8	2-Picoline <i>N</i> -oxide	46
9	3-Picoline <i>N</i> -oxide	45
10	Quinoline <i>N</i> -oxide	33
11	DMAP	27
12	DBN	34
13	DBU	43
14	Triphenylphosphine	35

^aDetermined by ¹H NMR spectroscopic analysis.

Many of the *N*-oxides investigated are strongly hygroscopic solids or are supplied as a hydrate. Therefore, to discount the reaction being promoted or negatively influenced by adventitious water, the bromination of *tert*-butylbenzene was repeated only in the presence of 20 mol% water (Scheme 301). No improvement upon the background rate was observed, with just 4% conversion into **586** occurring after 4 hours (*cf.* 4%, no catalyst), and thus the presence of small quantities of water does not appear to influence the reaction. However, it should be noted that small quantities of other unidentified species were observed within the ¹H NMR spectrum but, based on the alkyl signals, these impurities do not appear to be derived from the starting material.



Scheme 301. Investigating the effect of water on the bromination of *tert*-butylbenzene (**585**) with bromine.

From the organocatalyst screen, 4-picoline *N*-oxide was identified as the most active catalyst under the conditions studied. Consequently, this cheap, readily available and easy to handle species was selected for further optimisation. Initially, an extended reaction time of 24 hours was examined to determine whether the bromination would proceed to completion. Interestingly, only 61% conversion into **586** was attained (Table 39, entry 3), which represents a mere 12% increase in reaction progress after an additional 20 hours (*cf.* 49% conversion, 4 hours). Thus, it was proposed that catalyst deactivation may be occurring *via* protonation of the *N*-oxide under the highly acidic reaction conditions; arising from the evolution of hydrogen bromide as the reaction proceeds. In further support of this hypothesis, it was found that 30% conversion into **586** could be achieved after the reduced reaction time of 80 minutes (Table 39, entry 1).

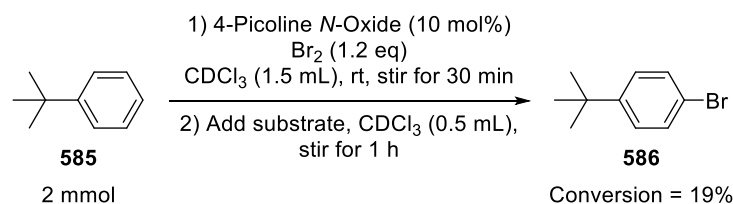
Table 39. Variation of reaction time for the 4-picoline *N*-oxide catalysed bromination of *tert*-butylbenzene (**585**) with bromine.

CC(C)(C)c1ccccc1 **585** (2 mmol) $\xrightarrow[\text{CDCl}_3 (2 \text{ mL}), \text{rt, time}]{\text{Br}_2 (1.2 \text{ eq}), \text{4-Picoline } N\text{-Oxide (10 mol\%)}}$ CC(C)(C)c1ccc(Br)cc1 **586**

Entry	Time (h)	Conversion (%) ^a
1	80 (min)	30
2	4	49
3	24	61
4 ^b	24	5

^aDetermined by ¹H NMR spectroscopic analysis. ^bNo catalyst.

It was considered that if formation of the proposed *N*-oxide bromine complex is the rate-determining step, the reaction rate may be enhanced by preforming this reactive brominating species. Therefore, 4-picoline *N*-oxide was treated with bromine for 30 minutes to encourage formation of the active complex prior to addition of the substrate. Unexpectedly, this approach slightly reduced the level of conversion into **586** after 1 hour relative to the original procedure (Scheme 302, *cf.* 19% *vs* 29%); suggesting that in fact an undesirable reaction may be occurring between the *N*-oxide and bromine. This result indicates that preforming the *N*-oxide bromine complex is not necessary and may not be rate-determining. Interestingly, upon addition of bromine to many of the catalysed systems previously detailed within Table 38, a fine, light coloured precipitate was immediately observed suspended in solution, which subsequently dissolved giving a homogeneous mixture. In combination these observations suggest that formation of the *N*-oxide complex is very rapid.


Scheme 302. Examining the effect of treating 4-picoline *N*-oxide with bromine prior to addition of *tert*-butylbenzene (**585**).

In an attempt to elucidate information on the interaction between 4-picoline *N*-oxide and bromine, a 1:1.2 mixture of these reagents in deuterated chloroform was analysed by ¹H NMR spectroscopy after 5 minutes and 1 hour (Figure 72). Upon comparison of these spectra with that obtained for 4-picoline *N*-oxide alone, it was observed that all peaks had shifted downfield after both time

periods, which may be indicative of complex formation. Additionally, after 1 hour an additional peak was observed at 4.46 ppm, which may be attributed to species **587** formed *via* radical induced benzylic bromination of 4-picoline *N*-oxide. Specifically, 12% of the *N*-oxide catalyst was found to exist as **587**, which was established by comparison of the relative integrals for the peaks at 2.52 and 4.46 ppm for the parent and brominated species respectively. This competitive process may account for the reduced catalytic activity observed when the *N*-oxide and bromine are premixed, as bromination of the catalyst may influence its electronics and would also consume some of the bromine reagent.

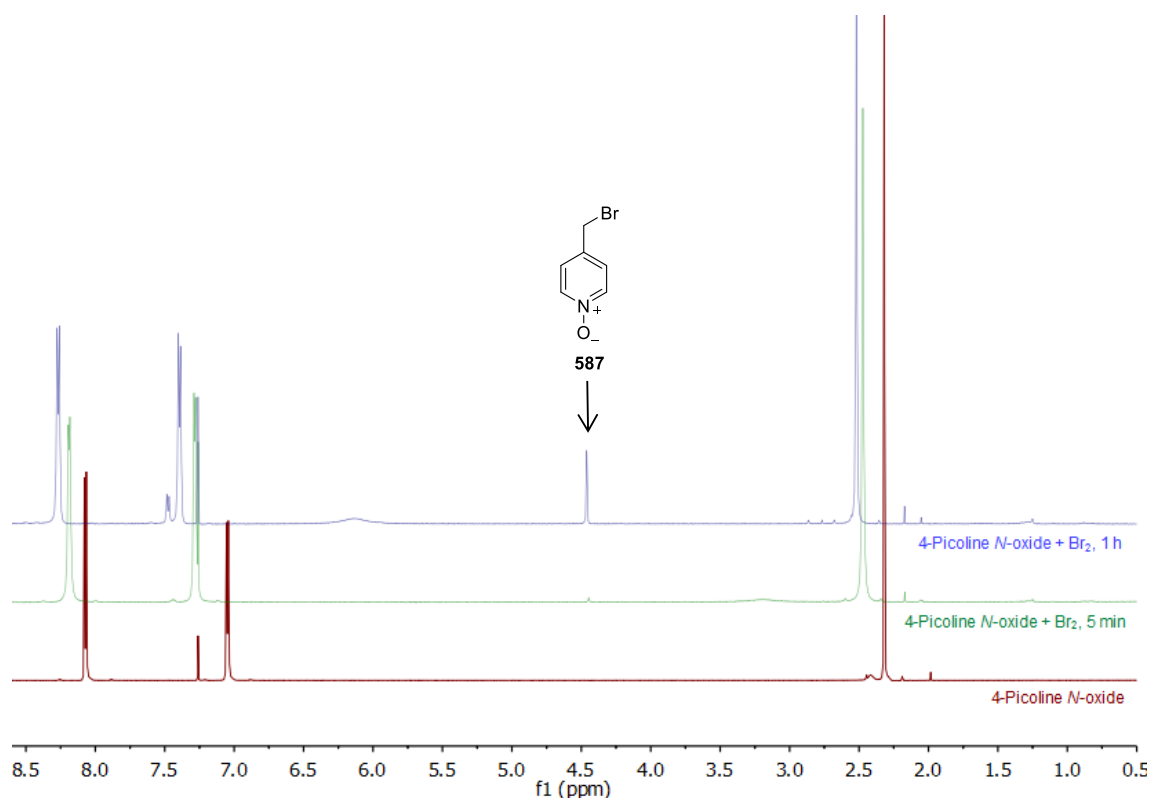
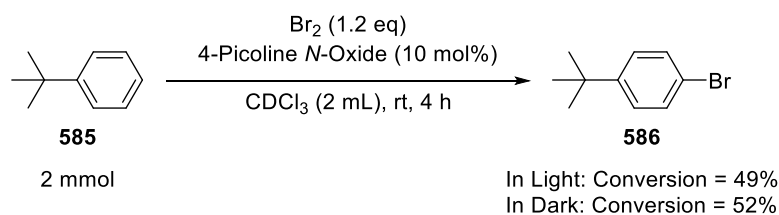


Figure 72. Overlaid 400/500 MHz ¹H NMR spectra obtained in CDCl₃ depicting the interaction and reaction of 4-picoline *N*-oxide with elemental bromine.

To prevent this competitive, radical induced event occurring and determine whether there was any associated improvement in reaction rate, the standard bromination reaction was repeated with the exclusion of light. However, no significant improvement in reaction progress was observed (Scheme 303, *cf.* 52% *vs* 49%), suggesting that species **587** does not form during the reaction in the presence of the substrate.



Scheme 303. Examining the effect of light upon the 4-picoline *N*-oxide catalysed bromination of *tert*-butylbenzene (**585**).

As previously detailed, deactivation of the *N*-oxide catalyst may also occur due to the increasingly acidic conditions as the reaction progresses. Efforts were made to neutralise the evolved hydrogen bromide and thereby prevent catalyst deactivation through the addition of both inorganic and organic bases; namely NaOH, K_2CO_3 and triethylamine (Table 40). Unfortunately, the presence of such additives resulted in the catalytic effect being nullified, with the rate reverting to the background, uncatalysed level. Upon addition of bromine to the system containing triethylamine, a particularly vigorous and exothermic reaction prevailed; presumably due to the formation of a 1:1 charge transfer complex between the triethylamine and bromine (~94%), which has been extensively reported within the literature.⁶⁹¹

Table 40. Effect of bases on the 4-picoline *N*-oxide catalysed bromination of *tert*-butylbenzene (**585**) with bromine.

Entry	Additive	Conversion (%) ^a
1	No additive	29
2	NaOH	2
3	K_2CO_3	5
4	Et_3N	3

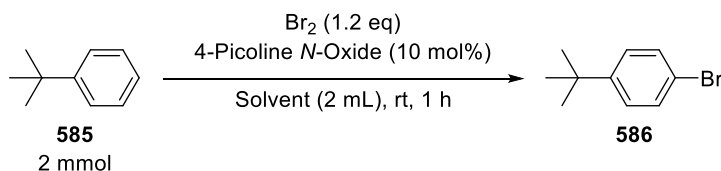
^aDetermined by ^1H NMR spectroscopic analysis.

To control the acidity of the reaction medium the use of a buffer was also examined. It was found that by employing a biphasic solvent system containing a 1:1 mixture of deuterated chloroform and aqueous sodium phosphate buffer (0.5 M), the extent of bromination could be significantly improved. Whilst only 29% conversion into **586** was achieved in deuterated chloroform, this was almost doubled to 50% in the presence of the biphasic system (Table 41, entry 10). Interestingly, the application of a buffer did not significantly promote the uncatalysed reaction (3% conversion). Based on the success of this reaction medium, alternative solvent systems were subsequently

examined to see whether further improvement could be afforded. Ether based solvents, such as THF, diethyl ether and methyl *tert*-butyl ether (MTBE) were avoided due to the potential for exothermic ether cleavage by evolved hydrogen bromide.⁶⁹²

Interestingly, the degree of reaction progress was found to be highly sensitive to the solvent identity, with a large disparity in conversions observed (Table 41). Highly polar solvents gave superior conversion into **586** (Table 41, entries 1-3), as did the most non-polar solvent, pentane (Table 41, entry 9). Within polar media, the observed increase in conversion may be attributed to the high solubility of hydrogen bromide. As electrophilic aromatic brominations may be acid promoted,^{693,694} the evolved hydrogen bromide by-product may induce an autocatalytic effect, which would also account for the enhancement in the background rates (e.g. water: 41%; acetonitrile: 50%). Alternatively, this rate enhancement may be attributed to stabilisation of the Wheland intermediate in the more polar solvents. Conversely, hydrogen bromide would be poorly solubilised in pentane; minimising the acid promoted bromination pathway but enhancing catalytic activity by circumventing protonation and therefore deactivation of the catalyst. This is consistent with the negligible background reaction observed in pentane (1%) and the greatly enhanced reaction rate upon addition of *N*-oxide. Due to the potential solubility issues that may present when using a solid substrate in the highly polar or non-polar solvents, a series of 1:1 aqueous biphasic systems were also examined (Table 41, entries 10-16). In all instances, good conversion (50-62%) into **586** was achieved and water was found to be equally as effective as the sodium phosphate buffer. Whilst a 1:1 mixture of pentane:water gave the best result of any biphasic system (Table 41, entry 16), the same solubility issues apply. The next most efficient system, involving deuterated chloroform was discounted on economic grounds (Table 41, entry 13). Consequently, a chloroform (CHCl₃):water biphasic mixture was deemed a suitable alternative; achieving high conversion with the greatest degree of catalytic effect relative to the uncatalysed background reaction with bromine (Table 41, entry 12).

Table 41. Solvent screen for the 4-picoline *N*-oxide catalysed bromination of *tert*-butylbenzene (585**) with bromine.**



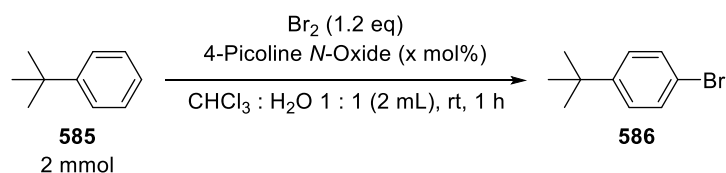
Entry	Solvent	Conversion (%) ^a
1	Buffer ^b	85
2	H ₂ O	85
3	MeCN	47

4	MeOH	10
5	EtOAc	11
6	CHCl ₃	29
7	CDCl ₃	29
8	CH ₂ Cl ₂	27
9	Pentane	57
10	CDCl ₃ : Buffer ^b (1:1)	50
11	CH ₂ Cl ₂ : Buffer ^b (1:1)	54
12	CHCl ₃ : H ₂ O (1:1)	54
13	CDCl ₃ : H ₂ O (1 :1)	58
14	CH ₂ Cl ₂ : H ₂ O (1:1)	54
15	MeCN : H ₂ O (1:1)	51
16	Pentane : H ₂ O (1:1)	62

^aDetermined by ¹H NMR spectroscopic analysis. ^bAqueous sodium phosphate buffer (0.5 M).

After screening the catalyst loading, 10 mol% of 4-picoline *N*-oxide was found to be optimal (Table 42, entry 2). Interestingly, increasing the amount of catalyst any further was found to give inferior results (Table 42, entries 3-5). This may be due to competitive and undesired bromination of the catalyst or potential aggregation of the *N*-oxide species *via* hydrogen bonding interactions at higher catalyst concentrations, as described in Chapter 2.⁴³¹

Table 42. Varying the amount of 4-picoline *N*-oxide within the bromination of *tert*-butylbenzene (585) with bromine.



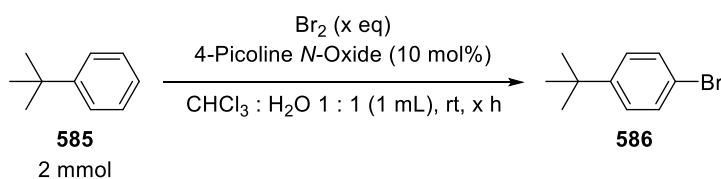
Entry	Catalyst loading (mol%)	Conversion (%) ^a
1	5	48
2	10	55
3	20	53
4	30	48
5	50	35

^aDetermined by ¹H NMR spectroscopic analysis.

The extent of reaction could be further improved by increasing the concentration of the whole system, with 70% conversion achieved by decreasing the total solvent volume to 1 mL (Table 43, entry 1). As may be anticipated, increasing the amount of bromine and extending the reaction

time also further enhanced the conversion (Table 43, entries 2-9). Complete consumption of the starting material could be successfully achieved by performing the reaction for 2 hours with 2.0 equivalents of bromine (Table 43, entry 8). Under such conditions, only 56% conversion into **586** was observed in the absence of a catalyst (Table 43, entry 9). Unfortunately, 100% conversion could not be attained with a smaller excess of bromine even after extended reaction times, which may be explained by catalyst deactivation over time (Table 43, entries 10 and 11).

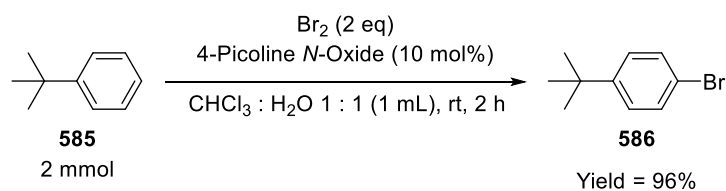
Table 43. Varying the reaction time and amount of bromine within the 4-picoline *N*-oxide catalysed bromination of *tert*-butylbenzene (**585**).



Entry	Equivalents of Br ₂	Time (h)	Conversion (%) ^a
1	1.2	1	70
2	1.3	1	74
3	1.5	1	85
4	1.2	4	83
5	1.5	4	93
6	2.0	4	100
7 ^b	2.0	4	58
8	2.0	2	100
9 ^b	2.0	2	56
10	1.2	48	83
11	1.5	24	97

^aDetermined by ¹H NMR spectroscopic analysis. ^bNo catalyst.

Under the fully optimised conditions, as detailed in Scheme 304, *tert*-butylbenzene (**585**) could be quantitatively converted into 1-bromo-4-(*tert*-butyl)benzene (**586**) and was subsequently isolated in an excellent 96% yield. Thus, this methodology represents a mild method for the *para*-selective monobromination of *tert*-butylbenzene.

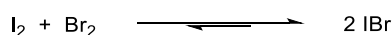


Scheme 304. 4-Picoline *N*-oxide catalysed synthesis of 1-bromo-4-(*tert*-butyl)benzene (**585**) using the optimised reaction conditions.

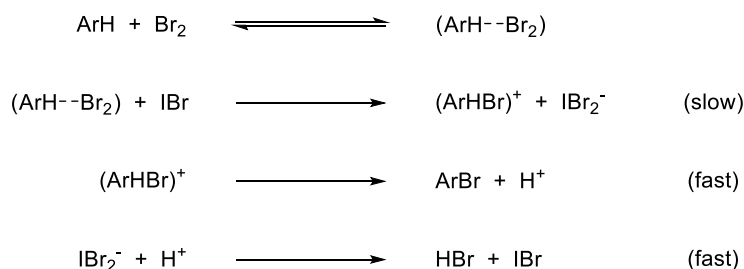
Pleasingly, these preliminary investigations demonstrate the potential of *N*-oxides to effectively catalyse the electrophilic aromatic bromination of mildly activated aryl species *via* electrophilic activation of the bromine reagent. From ^1H NMR studies it has been determined that the *N*-oxide and elemental bromine interact in solution. It is proposed that a *N*-oxide bromine complex is formed *in situ*,⁶⁸⁴ however the exact nature of the complex and its stoichiometry is yet to be elucidated. This adduct would function as an effective source of electrophilic bromine, with this system precluding the need for strong, metal-based Lewis acids, such as FeBr_3 , AlCl_3 or SbCl_3 .^{659,661} Nevertheless, a large excess of bromine is required to push the reaction to completion potentially due to deactivation of the catalyst.

4.3.2 Development of iodide catalysed methodology

Following success within the group in utilising iodide as an activating agent, it was of interest to determine whether iodide salts could also be employed as alternative catalysts within the aromatic bromination studied.⁶⁹⁵ It was hoped that such salts would not suffer from problems with deactivation, allowing for the amount of bromine to be reduced. The addition of iodine has long been known to promote electrophilic aromatic brominations, for which the *in situ* generated iodine monobromide (IBr) has been identified as the effective catalyst.⁶⁹⁶⁻⁷⁰⁰ An equilibrium exists between the iodine / bromine reagents and the iodine monobromide, for which the equilibrium typically favours the interhalogen species (Scheme 305).^{698,700} Extensive kinetics studies have determined that the iodine monobromide acts to polarise the Br-Br bond within the bromine arene adduct and remove the Br^- as IBr_2^- during the rate-determining step (Scheme 306).⁶⁹⁸⁻⁷⁰⁰ However, to the best of our knowledge easy to handle, crystalline iodide salts have not been investigated within this role.



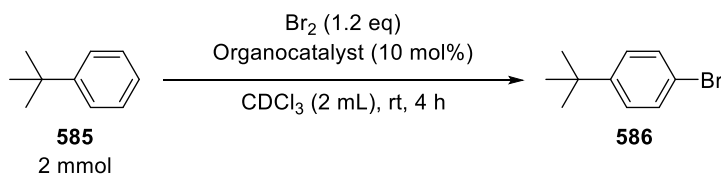
Scheme 305. Equilibrium that exists between iodine / bromine and iodine monobromide in solution.⁶⁹⁸



Scheme 306. Intermediate species involved in IBr catalysed electrophilic aromatic bromination reactions.^{698,699}

As detailed in Table 44, a range of iodide salts were screened to assess their catalytic ability within the bromination of *tert*-butylbenzene. Group 1 and 2 metal iodides in particular exhibited high catalytic activity, with conversions of 73-92% achieved after 4 hours (Table 44, entries 1-3 and 5). This compares favourably with the results achieved using *N*-oxides under analogous conditions (*cf.* Table 38). Whilst MgI₂ and NaI were found to be the most effective catalysts, these salts are particularly expensive and hygroscopic in nature respectively. Therefore, based on its relatively low cost and ease of handling, KI was identified as the most attractive option. Interestingly, the rate of reaction appeared to be dramatically reduced as the reaction progressed, as observed with *N*-oxide catalysts, with only a small increase in conversion observed after an additional 20 hours (Table 44, entry 4).

Table 44. Screen of iodide salts for the bromination of *tert*-butylbenzene (585) with bromine.



Entry	Identity of Organocatalyst	Conversion (%) ^a
1	LiI	73
2	NaI	86
3	KI	85
4	KI (24 h)	93
5	MgI ₂	92
6	ⁿ Bu ₄ N ⁺ I ⁻	49

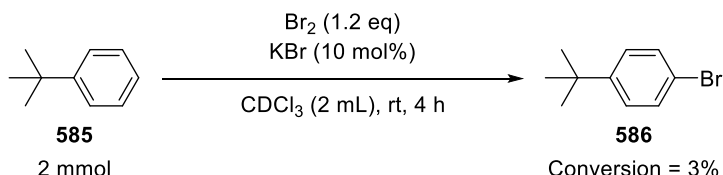
^aDetermined by ¹H NMR spectroscopic analysis.

Based on literature precedent, it is proposed that catalytically active IBr is generated *in situ* from the reaction of KI with bromine (Scheme 307). As KBr would be formed as a by-product from this salt metathesis, the background reaction was run in the presence of this potassium salt to

discount its involvement or that of the metal cation in promoting the desired bromination (Scheme 308). As may be expected, no rate enhancement was observed (3% conversion).

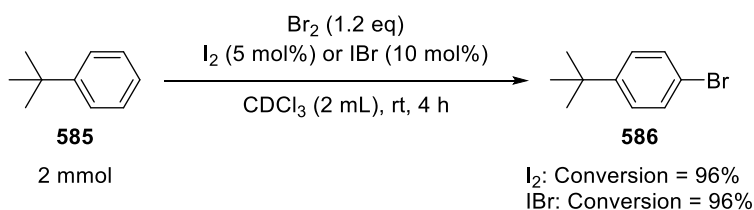


Scheme 307. Potential *in situ* generation of IBr from the reaction of KI with bromine.



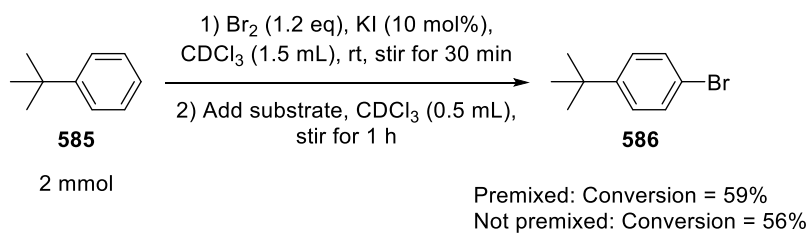
Scheme 308. Examining the effect of KBr on the bromination of *tert*-butylbenzene (**585**) with bromine.

To provide evidence that IBr is functioning as the catalytically active species, the reaction was repeated separately in the presence of 5 mol% I_2 or 10 mol% of IBr (Scheme 309). Accordingly, 96% conversion was achieved in both instances, suggesting that IBr is in fact the active catalyst; generated *in situ* from KI *via* the formation of I_2 (Scheme 307). The slightly reduced conversion observed using KI (*cf.* 85% *vs* 96%) may in part be attributed to consumption of the bromine reagent (~8%) to form the interhalogen catalyst or could potentially be the result of *in situ* generated KBr and IBr reacting to form inactive KIBr_2 . The latter may also account for the significant drop off in reaction rate observed with time. Nevertheless, KI is much easier to handle than I_2 and the low melting and corrosive interhalogen compound (IBr), which is commercially prepared from the reaction of elemental bromine with iodine.



Scheme 309. Exploring the effect of I_2 and IBr on the bromination of *tert*-butylbenzene (**585**) with bromine.

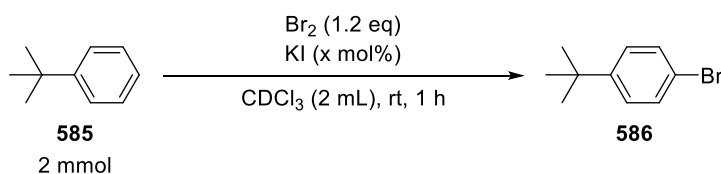
An induction period arising from slow generation of I_2 and consequently IBr is a third possibility for the discrepancy observed for the catalytic activity of KI. To discount this as a factor in the reduced conversion, KI and Br_2 were mixed for 30 minutes prior to addition of the substrate (Scheme 310). However, a negligible difference in conversion was achieved (*cf.* 59% *vs* 56%) and therefore it may be concluded that I_2 generation under the reaction conditions is rapid.



Scheme 310. Examining the effect of treating KI with bromine prior to addition of *tert*-butylbenzene (**585**).

Examination of the catalyst loading revealed that utilising 10 mol% of KI was most favourable (Table 45, entry 3), with lower loadings resulting in significantly reduced conversions and greater amounts of catalyst giving a disproportionately small improvement in reaction progress (Table 45). Interestingly, excess KI has previously been utilised as a quench for bromination reactions performed using elemental bromine. The continued success of this methodology at high catalyst loading was therefore particularly pleasing.

Table 45. Varying the amount of KI within the bromination of *tert*-butylbenzene (**585**) with bromine.



Entry	Catalyst loading (mol%)	Conversion (%) ^a
1	No catalyst	3
2	5	30
3	10	56
4	20	54
5	30	58
6	50	61

^aDetermined by ¹H NMR spectroscopic analysis.

As previously observed for *N*-oxide catalysed reactions, the bromination performed well in polar solvents (Table 46, entries 1 and 2) as well as in aqueous biphasic solvent systems (Table 46, entries 9 and 10). However, in this instance a superior conversion of 62% was achieved using DCM alone as the reaction medium (Table 46, entry 7). Curiously, the reaction performed in chloroform (CHCl₃) resulted in extremely low conversion into **586** (Table 46, entry 5), particularly when compared with other related chlorinated solvents, such as its deuterated analogue (CDCl₃) and DCM (Table 46, entries 6 and 7). Chloroform is known to be the more acidic medium and its C-H bond is much weaker and more labile than the equivalent bond in the

other two solvents. These properties may be responsible for the observed disparity in conversion, however the exact reason remains unclear.

Table 46. Solvent screen for the KI promoted bromination of *tert*-butylbenzene (585) with bromine.

585 (2 mmol) → 586

Entry	Solvent	Conversion (%) ^a
1	H ₂ O	49
2	MeCN	47
3	MeOH	18
4	EtOAc	16
5	CHCl ₃	9
6	CDCl ₃	54
7	CH ₂ Cl ₂	62
8	Pentane	34
9	CDCl ₃ : H ₂ O (1:1)	49
10	CH ₂ Cl ₂ : H ₂ O (1:1)	44

^aDetermined by ¹H NMR spectroscopic analysis.

From further optimisation studies it was determined that almost quantitative conversion could be achieved by increasing the concentration to 2 mmol/mL (Table 47, entry 2) and subsequently increasing the reaction time to two hours (Table 47, entry 7). Under these optimised conditions the background reaction was found to proceed to a much lower 33% conversion relative to the uncatalysed reaction for the 4-picoline *N*-oxide system (Table 47, entry 8).

Table 47. Varying the reaction time and amount of bromine within the KI promoted bromination of *tert*-butylbenzene (585).

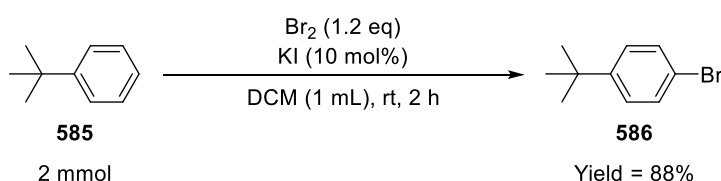
585 (2 mmol) → 586

Entry	Equivalents of Br ₂	Time (h)	Conversion (%) ^a
1	1.1	1	95
2	1.2	1	97
3 ^b	1.2	1	27
4	1.3	1	96

5	1.1	2	96
6 ^b	1.1	2	31
7	1.2	2	99
8 ^b	1.2	2	33

^aDetermined by ¹H NMR spectroscopic analysis. ^bNo catalyst.

Following work-up and purification, 1-bromo-4-(*tert*-butyl)benzene **586** was successfully isolated in 88% yield as the sole regioisomeric monobrominated product (Scheme 311). It is of interest to note that compared with the *N*-oxide catalysed methodology this procedure requires a much smaller excess of bromine to achieve high conversion. However, due to the additional washes required to remove the iodine by-product a slightly reduced yield was afforded.



Scheme 311. KI catalysed synthesis of 1-bromo-4-(*tert*-butyl)benzene (585**) using the optimised reaction conditions.**

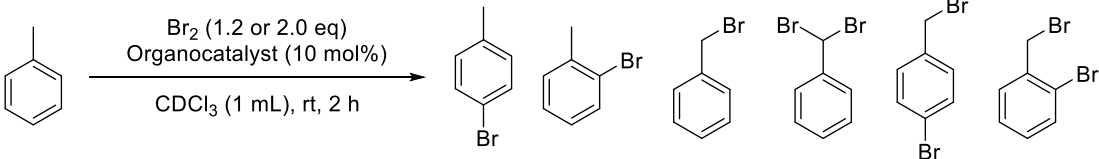
4.3.3 Optimisation of work-up procedure

With the exception of brominations performed in deuterated chloroform, the reactions were treated with 10% aqueous sodium thiosulfate solution to quench any unreacted bromine. Upon concentration of the organic phase *in vacuo*, a yellow residue was frequently observed in varying quantities, which was found to be relatively insoluble in many common organic solvents. Within such bromination reactions, an equivalent of hydrogen bromide is generated as a by-product relative to the amount of elemental bromine consumed, which when dissolved in water forms highly acidic hydrobromic acid. Thus, it is proposed that this pale yellow precipitate is elemental sulfur; formed from the decomposition of sodium thiosulfate under the acidic conditions.^{652,701,702} This decomposition pathway is well known and has been reported by Vaidyanathan and co-workers to account for the sulfur contamination observed in the Sandmeyer reaction for the synthesis of aryl iodides, which similarly employed sodium thiosulfate to quench the iodination reaction.^{652,701,702} Interestingly, the authors determined that sulfur formation could be minimised by performing a basic wash prior to addition of the sodium thiosulfate solution, with stronger bases such as NaOH affording superior results, or could be prevented entirely by employing an alternative reducing agent, such as sodium bisulfite.⁶⁵² Both of these methods of bromine removal were applied to the developed bromination conditions with promising results. Following its success, a sodium bisulfite quench was employed for all aforementioned product isolations, with the quoted yields obtained using this work-up.

4.3.4 Bromination of toluene

With the optimised conditions for both catalytic systems in hand, attempts were made to extend the developed methodologies to the bromination of toluene, which often suffers from competitive radical induced bromination, the formation of multiple regioisomeric products and in some instances polybromination.⁷⁰³⁻⁷⁰⁹ Accordingly, the uncatalysed bromination of toluene performed with both 1.2 and 2.0 equivalents of bromine gave benzylbromide **591** as the major product, with smaller amounts of the dibrominated species **592** also observed (Table 48, entries 1 and 3). The identity of such species was determined from the distinctive benzylic signals within the ¹H NMR spectra at 4.49 ppm and 6.64 ppm for **591** and **592** respectively, which are consistent with the literature values for these compounds.^{710,711} Although bromine was more successfully installed onto the ring using the larger excess of reagent, the majority of these compounds were dibrominated (**593** and **594**) and an extremely complex mixture of reaction products was observed (Table 48, entry 3). All species were again identified by ¹H NMR spectroscopy, with characteristic peaks in accordance with that reported within the literature.^{704,711-714} Interestingly, negligible benzylic bromination was found to occur in the presence of KI or 4-picoline *N*-oxide (Table 48, entries 2 and 4). In both instances, exclusively monobromination of the aromatic ring was instead observed; generating a mixture of both the *para*- and *ortho*-substituted products **589** and **590**.^{704,714} However, some selectivity for the *para*-substituted regioisomer was achieved. These reactions also proceeded with high consumption of the starting material, with the *N*-oxide promoted reaction giving 100% conversion (Table 48, entry 4).

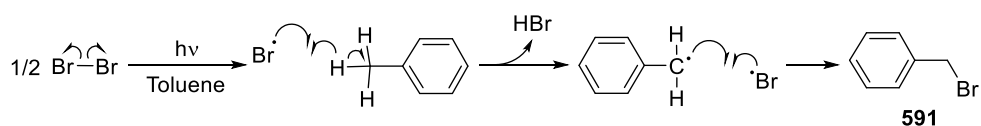
Table 48. Effect of KI and 4-picoline *N*-oxide on the bromination of toluene (**588**) with bromine.

											
588 2 mmol		589	590	591	592	593	594				
Entry	Equivalents of Br ₂	Identity of organocatalyst	Condition	588	589	590	591	592	593	594	
1	1.2	No catalyst	Light	1	-	-	80	17	1	1	
2	1.2	KI	Light	7	66	27	- ^a	-	-	-	
3	2.0	No catalyst	Light	1	2	4	67	10 ^b	12	3	
4	2.0	4-Picoline <i>N</i> -oxide	Light	-	64	36	- ^a	-	-	-	
5	1.2	No catalyst	Dark	78	11	6	5	-	-	-	
6	1.2	KI	Dark	6	66	28	-	-	-	-	

7	2.0	No catalyst	Dark	44	38	18	- ^a	-	-	-
8	2.0	4-Picoline	Dark	-	62	38	-	-	-	-
<i>N</i> -oxide										

The ratio of products was determined by ¹H NMR spectroscopic analysis. ^aNegligible amount observed (<1%). ^b1% of this product is *para*-brominated (**595**).

The formation of benzylbromide from toluene and elemental bromine, with the concomitant release of hydrogen bromide gas, is known to be a photochemically initiated reaction that proceeds *via* a free-radical chain mechanism (Scheme 312).⁷¹⁵ Such radical induced reactions typically show high selectivity for the cleavage of benzylic C-H bonds, due to the relatively low bond dissociation energy and the resonance stabilisation possible for the resulting radical.⁷¹⁶ Examples of this competitive photochemical reaction are prevalent within the literature.⁷⁰⁶⁻⁷⁰⁹ In order to confirm whether such a mechanism was being followed, the uncatalysed reaction was performed with light exclusion which, as expected, gave only minor quantities of benzylbromide **591** (Table 48, entries 5 and 7). Additionally, the reaction was performed in the presence of the organocatalysts with light exclusion to determine whether the same selectivity for the ring-substituted bromotoluene species **589** and **590** would be obtained. As detailed in Table 48, almost identical distributions of brominated products were achieved whether performing the reaction in the light or the dark (entries 2 and 4 *vs* entries 6 and 8). Thus, the presence of either catalyst renders electrophilic aromatic substitution more kinetically favourable than the undesired radical induced benzylic bromination; allowing for the selective functionalisation of the aromatic ring of toluene to be performed in the light.



Scheme 312. Free radical chain mechanism for the formation of benzyl bromide (**591**).⁷¹⁶

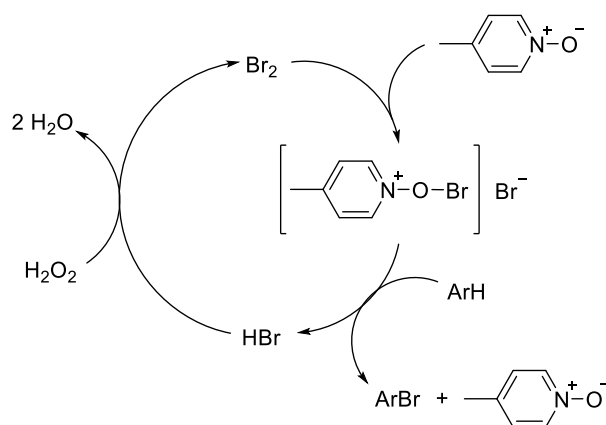
4.4 Conclusion

The application of *N*-oxides as organocatalysts has been successfully extended to electrophilic aromatic brominations. From these preliminary investigations, 4-picoline *N*-oxide has been identified as a successful catalyst for the regioselective monobromination of *tert*-butylbenzene. Employing a 10 mol% catalyst loading, quantitative conversion into the *para*-brominated product could be achieved after just 2 hours at room temperature using 2 equivalents of elemental bromine. Initial ¹H NMR spectroscopic studies are consistent with the formation of an *N*-oxide bromine complex, which may act as a reactive source of electrophilic bromine either *via* polarisation of the Br-Br bond, or formation of a cationic species. Excellent activity can also be achieved using 10 mol% of KI as the additive, with a smaller excess of bromine (1.2 equiv.) required to achieve comparable conversion. In this instance, IBr is thought to be generated *in situ* as the catalytic species. Both developed methodologies do not require the reactive species to be preformed in stoichiometric quantities, reducing the associated resource demand, and in both instances 1-bromo-4-(*tert*-butyl)benzene was successfully isolated in high yield. For the corresponding bromination of toluene, competitive benzylic bromination may be prevented by the inclusion of either catalytic species, which serve to lower the activation energy barrier for electrophilic aromatic bromination reactions below that of the undesired radical induced process.

4.5 Future work

Whilst the developed methodologies have been successfully applied to simple electron rich aromatics, further investigation is required to establish the substrate generality of these conditions. Achieving selective monobromination of electron deficient aromatics, which are generally unreactive to bromination in the absence of catalyst, and 5 membered heterocycles (furan, pyrrole and thiophene), which commonly suffer from polybromination, is of particular interest. Additionally, the potential for extending the *N*-oxide catalytic system to the analogous iodination reaction merits investigation.

As a consequence of employing elemental bromine as the reagent, the developed methodologies exhibit a maximum atom economy of 50% due to the generation of an equivalent of hydrogen bromide.^{681,717,718} Since this acidic by-product is corrosive and highly toxic as well as potentially playing a role in catalyst deactivation, the introduction of a process to aid with its removal and neutralisation is of paramount importance.^{636,681} In this regard, oxidative bromination has been identified as a suitable method for recycling the hydrogen bromide *in situ* (Scheme 313).^{630,636,668,670,718} More specifically, this biomimetic approach entails oxidation of the evolved hydrogen bromide back to bromine using an external oxidant, such as H₂O₂, which was originally inspired by the action of haloperoxidase enzymes in catalysing the formation of halogenating reagents from halide ions.^{630,636,668,670,717} Thus, not only would the use of an oxidant remove the offending by-product, it would also regenerate the bromine reagent, greatly improving its atom efficiency as well as eliminating the need for waste streams to be neutralised.^{681,717}



Scheme 313. Proposed catalytic cycle for the *N*-oxide catalysed oxidative bromination of aromatics.^{668,670}

Typically, brominations performed with elemental bromine are unrivalled based on cost and waste production considerations.^{657,668} However, the low cost of H₂O₂, the low molar mass of the HBr-H₂O₂ couple and the production of water as the sole by-product would mean that this

oxidative bromination could be competitive in relation to these important factors.^{636,657,668,670,717,718} Additionally, this approach should be compatible with the systems identified, as it was found that the electrophilic aromatic bromination proceeds well in aqueous and biphasic solvent systems. However, the potential decomposition of hydrogen peroxide by the halogen would need to be considered.⁶⁷⁰

5 Experimental

5.1 General Experimental Information

Unless preparative details are given, reagents and solvents were obtained from commercial suppliers, specifically: Acros Organics, Alfa Aesar, Fisher Scientific, Fluorochem, Sigma Aldrich and TCI and were used directly as received without further purification. *m*CPBA ($\leq 77\%$, product number: 273031) was purchased from Sigma Aldrich. For the purpose of calculations 4-dimethylaminopyridine *N*-oxide (DMAPO) was assumed to be anhydrous. All reactions were performed without air exclusion, at room temperature and with magnetic stirring unless otherwise stated. Anhydrous MgSO_4 or Na_2SO_4 were used as drying agents for organic solutions, filtrations were performed using Whatman cellulose filter paper and a rotary evaporator was used routinely to remove solvent under vacuum. Petrol refers to petroleum ether with a boiling range of 40-60 °C. Aqueous solutions were prepared using deionised water. 0.5 M sodium phosphate buffer was prepared by mixing 0.5 M aqueous solutions of Na_2HPO_4 and NaH_2PO_4 in a 61.5:38.5 ratio.

Thin layer chromatography (TLC) was carried out on Macherey-Nagel aluminium-backed plates, which are precoated with ALUGRAM® SIL G/UV254. Compounds were visualised by quenching of UV fluorescence at 254 nm or, where necessary, by staining with potassium permanganate, phosphomolybdic acid (PMA) or vanillin dip followed by gentle heating. Purification by flash column chromatography was performed using high-purity grade 60 Å silica gel (60 Å pore size, 40-75 µm particle size) purchased from Sigma Aldrich or 60 Å silica gel (60 Å pore size, 40-63 µm particle size) purchased from Fluorochem. Samples were loaded as saturated solutions made up in either the column eluent or a suitable solvent. Purification by distillation was performed using Kugelrohr distillation apparatus under reduced pressure.

Capillary melting points were determined using a Stuart digital SMP10 melting point apparatus and are reported to the nearest degree Celsius. An Optical Activity Ltd AA-10 Series Automatic Polarimeter with a path length of 1 dm was used to measure optical rotations, with concentration (*c*) quoted in g/100 mL.

Nuclear Magnetic Resonance (NMR) spectroscopy experiments were performed in deuterated solvent at 298 K on either a Brüker Avance 250, 300, 400 or 500 MHz spectrometer or a Agilent ProPulse 500 MHz spectrometer, with proton decoupling for all ^{13}C NMR spectra. ^1H and ^{13}C NMR chemical shifts, δ , are quoted in parts per million (ppm) and where possible are referenced against the residual, non-deuterated solvent peak.⁶¹⁶ The following abbreviations are used to denote the signal multiplicities and general assignments: singlet (s), doublet (d), triplet (t), quartet

(q), septet (sept.), multiplet (m), doublet of doublets (dd), doublet of doublet of doublets (ddd), doublet of triplets (dt), triplet of doublets (td), triplet of triplets (tt), septet of doublets (sept.d), broad (br.) and apparent (app.). The coupling of unsymmetrical *para*-disubstituted benzenes and 4-substituted pyridines, which contain magnetically inequivalent protons (AA'BB' systems), are for simplicity described as a doublet with the '*J*' coupling calculated from the spacing between the most intense signals; where these resonances are of low intensity or are not well defined the signal is reported as a multiplet. Where known, coupling constants (*J*) are reported to the nearest 0.1 Hz. The ratio of formamide rotamers was determined by comparison of the integrals for equivalent peaks within the ¹H NMR spectra and (m) and (M) are used to denote minor and major rotamers respectively within the ¹³C NMR assignment. Where analogous compounds have been reported within the literature, comparisons to published spectroscopic data were used to aid NMR assignments.

A PerkinElmer Spectrum 100 FTIR spectrometer with Universal ATR FTIR accessory was used to record infrared (IR) spectra; with samples run neat and the most relevant, characteristic absorbances quoted as ν in cm⁻¹. The spectrometer was calibrated prior to each sample being run.

High resolution mass spectrometry (HRMS) results were typically acquired on an externally calibrated Bruker Daltonics micrOTOFTM time-of-flight mass spectrometer coupled to an electrospray source (ESI-TOF). Calibration was achieved using a sodium formate solution. Samples were introduced either by syringe pump or flow injection using an autosampler in an Agilent 1100 LC system. Molecular ions were detected in positive mode as either the protonated or sodiated form and Bruker Daltonics software, DataAnalysisTM, was used to process the data. Alternatively, data was acquired externally at the EPSRC National Mass Spectrometry Facility, Swansea University, using a Thermo Scientific LTQ Orbitrap XLTM Fourier Transform Mass Spectrometer fitted with a nanoelectrospray ionisation source (nESI).

Gas chromatography mass spectrometry (GCMS) analysis for 1-bromo-4-(*tert*-butyl)benzene **586** was conducted on an Agilent 7890B Gas Chromatograph coupled to an Agilent 5977A inert Mass Selective Detector (MSD) with a Triple-Axis Detector. An Agilent DB-FFAP capillary column (a nitroterephthalic-acid-modified polyethylene glycol (PEG) column of length: 30 m, internal diameter: 0.25 mm, film thickness: 0.25 μ m) was used as the stationary phase, with helium as the mobile phase (flow rate: 1.2 ml/min). An Agilent 7693 Autosampler was used to inject 1 μ L of sample, with an inlet temperature of 250 °C. The oven was initially set at 40 °C and was ramped at 20 °C/min until it reached 250 °C, after which it was held for 5.5 minutes. Retention time (*t_R*) is quoted in minutes and the ion/fragment assignment and relative peak intensity are given in parentheses. GCMS analysis of vinyl esters was performed externally at the EPSRC National

Mass Spectrometry Facility, Swansea University on a Waters GCT Premier™ time of flight mass spectrometer employing ammonia chemical ionisation (CI, NH₃).

Single crystal X-ray crystallographic data was obtained on a Nonius KappaCCD diffractometer at 150(2) K using Mo-K α radiation ($\lambda = 0.71073$ Å). The structure was solved by direct methods, with refinement of F^2 data against all reflections using SHELXL-97 suite of programs. Crystal structure data was obtained by Dr Mary Mahon.

5.2 Experimental procedures and compound characterisation data for Chapter 2

5.2.1 General procedures for starting material synthesis

General Procedure 1: *Synthesis of 4-substituted aminopyridines*

The following was based on a literature procedure published by Williams *et al.*⁴²⁴ To a stirring mixture of $\text{Zn}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ (0.149 g, 0.5 mmol, 10 mol%) and the appropriate cyclic amine (5 mmol) in MeCN (5 mL) was added 4-chloropyridine (0.568 g, 5 mmol) in a single portion. The resulting mixture was then heated at 75 °C for 24 hours. After allowing the reaction mixture to cool to room temperature, the solvent was removed *in vacuo*. The crude product was then purified by flash column chromatography (5% methanolic ammonia in CH_2Cl_2) to afford the desired substituted pyridine.

General procedure 2a: *Synthesis of α,β -unsaturated methyl ketones using morpholinium trifluoroacetate 389*

The following was based on a literature procedure published by List *et al.*⁴⁵⁰ To a stirring solution of the appropriate aldehyde (30 mmol) in acetone (75 mL) was added amine salt **389** (1.207 g, 6 mmol, 20 mol%). The resulting mixture was then heated under reflux for 18 hours. After allowing the reaction mixture to cool to room temperature, saturated aqueous NaHCO_3 solution and EtOAc were added and the two phases were separated. The aqueous phase was extracted three times with EtOAc and the combined organic phases were dried over MgSO_4 , filtered and concentrated *in vacuo*. The crude product was then purified by flash column chromatography, with the eluent as specified, to afford the desired α,β -unsaturated ketone.

General procedure 2b: *Synthesis of α,β -unsaturated methyl ketones using NaOH*

The following was based on a literature procedure published by Deng *et al.*⁷¹⁹ To a stirring solution of the appropriate aldehyde (20 mmol) in acetone (4 mL, 55 mmol) and H_2O (2 mL) was added 10% aqueous NaOH solution (0.5 mL) dropwise over 30 minutes at 0 °C. Upon complete addition, the resulting mixture was allowed to warm gradually to room temperature and was stirred for 24 hours. The reaction was then quenched with aqueous 1 M HCl, with sufficient quantities added to adjust the solution to pH 4, and extracted three times with CH_2Cl_2 . The combined organic phases were washed sequentially with saturated aqueous NaHCO_3 solution and brine before being dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude product was then purified by either Kugelrohr distillation or flash column chromatography, as specified, to afford the desired α,β -unsaturated ketone.

General procedure 2c: Synthesis of chalcone derivatives

The following was based on a literature procedure published by Xu *et al.*⁷²⁰ To a stirring solution of the appropriate aldehyde (20 mmol) and acetophenone derivative (20 mmol) in EtOH (10 mL) was added slowly 10% aqueous NaOH solution (5 mL) at 0 °C. Upon complete addition, the reaction mixture was allowed to warm gradually to room temperature and was stirred for a further hour. The precipitate was then collected by vacuum filtration and purified by either flash column chromatography or recrystallization from EtOH, as specified, to afford the desired α,β -unsaturated ketone.

General Procedure 3: Synthesis of sodium benzoate salts

To a stirring solution of NaOH (0.160 g, 4 mmol) in the minimum amount of H₂O was added the appropriate benzoic acid (4 mmol) portionwise to control the exotherm. Once all of the solid had dissolved, the solution was left stirring for 2 hours at room temperature. The H₂O was then removed *in vacuo* (azeotroped with toluene) to afford cleanly the desired sodium benzoate salt.

5.2.2 Standard work-up procedure

Within sections 5.2.4 – 5.2.9, any method employing the standard work-up procedure is referring to the following protocol:

At the specified point, the reaction was quenched with saturated aqueous NaHCO₃ solution, with sufficient quantities added to ensure that all of the precipitate had dissolved, and an equal quantity of EtOAc was then added. The resulting layers were separated and the organic phase was washed with a further portion of saturated aqueous NaHCO₃ solution. The aqueous washings were then extracted with EtOAc and the combined organic phases were dried over MgSO₄, filtered and concentrated *in vacuo*.

Where applicable, conversions were determined by analysis of the ¹H NMR spectra obtained in CDCl₃ for the crude reaction mixture. Specifically, for oxidations of (*E*)-4-phenyl-3-buten-2-one, the ratio of species present was determined by comparison of the integrals for the peaks at 4.01, 5.56, 5.98, 6.05, 6.39, 6.73 and 7.76 ppm attributable to epoxy ketone **338**, epoxy ester **339**, carboxylic acid **353**, aldehyde **341**, vinyl ester **337**, ketone **336** and formate ester **354** respectively.

5.2.3 Iodometric titration to determine the purity of *m*CPBA

To a conical flask containing a solution of NaI (1.500 g, 10 mmol) in water (50 mL) was added glacial acetic acid (5 mL) and CHCl₃ (5 mL). A known amount of *m*CPBA (0.300 g) was dissolved in CHCl₃ (3.8 mL) and the resulting solution was added to the NaI mixture. The

liberated iodine was then titrated against 0.1 N aqueous Na₂S₂O₃ solution (3.953 g dissolved in 250 mL H₂O).

1 mL of 0.1 N Na₂S₂O₃ \equiv 0.0086 g of *m*CPBA

Attempt 1	Attempt 2	Attempt 3
27.7 mL \equiv 0.238 g \equiv 79%	27.5 mL \equiv 0.237 g \equiv 79%	27.9 mL \equiv 0.240 g \equiv 80%

*m*CPBA is supplied in \leq 77% purity. Based on the titration results, *m*CPBA was assumed to be 77% pure for all proceeding reactions. However, it should be noted that several different batches of this reagent were used.

5.2.4 General procedures for the optimisation of Baeyer-Villiger methodology

General Procedure 4: Optimisation screens (Sections 2.3.1 and 2.3.3 and Scheme 216)

To a vigorously stirring mixture of the appropriate oxidant in solvent was added any specified organocatalyst and/or additive and (*E*)-4-phenyl-3-buten-2-one (0.146 g, 1 mmol). The resulting mixture was stirred at room temperature (or -10 °C, where stated) for the specified period of time, after which the standard work-up procedure was then applied.

General procedure 5: Variation of work-up procedure (Section 2.3.3)

To a vigorously stirring suspension of *m*CPBA (0.336 g, 1.5 mmol, 1.5 equiv.) in toluene (3.5 mL) was added DMAP (0.024 g, 0.2 mmol, 20 mol%) and (*E*)-4-phenyl-3-buten-2-one (0.146 g, 1 mmol). The resulting mixture was stirred at room temperature for 2 hours. The specified work-up reagent was then added to quench the reaction and the mixture was stirred for 20 minutes. After this period, the mixture was filtered, washed through with EtOAc and the liquors were concentrated *in vacuo*.

Work-up reagents include: Activated charcoal: DARCO® 100 mesh powder (1 g), Na₂CO₃ (2 g), cyclohexene (5 mL), triethylamine (5 mL), Na₂HPO₄ (2 g), Na₂S₂O₃•5H₂O (2 g), Na₂SO₃ (2 g) or NaHCO₃ (5 g).

General procedure 6: Establishing the role of the *N*-oxide (Schemes 172 and 176)

To a vigorously stirring mixture of the appropriate *N*-oxide (1.0 equiv.) in toluene was added benzoic acid if specified and (*E*)-4-phenyl-3-buten-2-one (0.146 g, 1 mmol). The resulting mixture was stirred at room temperature for the specified period of time, after which the standard work-up procedure was then applied.

General procedure 7: *In situ* reaction under the optimised conditions (Table 11)

To a vigorously stirring suspension of *m*CPBA (0.168 g, 0.75 mmol, 1.5 equiv.) in d_8 -toluene (1.75 mL) was added any specified organocatalyst (20 mol%) and (*E*)-4-phenyl-3-buten-2-one (0.073 g, 0.5 mmol). The resulting mixture was stirred at room temperature for 2 hours. The reaction was then diluted with sufficient quantities of d_8 -toluene to ensure that all of the precipitate had dissolved and the mixture was homogenous. An aliquot of the reaction mixture was then removed for analysis by ^1H NMR spectroscopy, with spectra obtained on a 500 MHz spectrometer. The ratio of species present was determined by comparison of the integrals for the peaks at 3.47, 5.39, 5.74, 5.97, 6.23, 6.46 and 7.80 ppm attributable to epoxy ketone **338**, epoxy ester **339**, acid **353**, aldehyde **341**, vinyl ester **337**, ketone **336** and formate ester **354** respectively.

5.2.5 Procedures for mechanistic studies**General procedure 8: *Deuterium incorporation experiment using d_1 -acetic acid (Scheme 181)***

To an NMR tube containing a d_8 -toluene solution (0.5 mL) of the specified organocatalyst (0.057 mmol, 20 mol%) was added a solution of (*E*)-4-phenyl-3-buten-2-one (0.042 g, 0.286 mmol) in d_8 -toluene (0.5 mL). The reaction mixture was then treated with d_1 -acetic acid (0.030 mL, 0.520 mmol, 1.82 equiv.) and was left at room temperature for 2 hours. The extent of deuterium incorporation was then determined by analysis of the ^1H and ^2H NMR spectra obtained for the crude reaction mixture.

Result: No deuterium incorporation observed.

General procedure 9: *Deuterium incorporation experiment using d_4 -methanol (Scheme 182)*

To a d_4 -methanol solution (0.5 mL) of (*E*)-4-phenyl-3-buten-2-one (0.263 g, 1.8 mmol) in an NMR tube was added the required organocatalyst (5 mol%). After leaving the reaction mixture at room temperature for 24 hours, the deuterium incorporation was determined by analysis of the ^1H and ^2H NMR spectra obtained for the crude reaction mixture.

Result: DMAP (0.011 g, 0.09 mmol, 5 mol%): 20% deuterium incorporation observed at the methyl position only. ^1H NMR (400 MHz, CD_3OD): δ_{H} = 7.61-7.53 (3H, m, PhCH and 2 x PhH), 7.41-7.34 (3H, m, PhH), 6.73 (1H, d, J = 16.4 Hz, C(O)CH), 2.36-2.29 (2.41H, m, CH_3 CH_2D and CHD_2); ^2H NMR (400 MHz, CD_3OD): δ_{D} = 2.32 (s), 2.29 (s), 2.25 (s) (methyl isotopologues: CH_2D , CHD_2 , CD_3)

DMAPO (0.012 g, 0.09 mmol, 5 mol%): No deuterium incorporation observed.

General procedure 10: *Trapping of enol intermediate 364 via acylation (Scheme 183)*

To a d₈-toluene solution (0.75 mL) of (*E*)-4-phenyl-3-buten-2-one (0.018 g, 0.125 mmol) in an NMR tube was added benzoic acid (0.015 g, 0.125 mmol, 1.0 equiv.) if specified and acetic anhydride (0.012 mL, 0.125 mmol) followed by the required organocatalyst (0.131 mmol, 1.05 equiv.). After leaving the reaction mixture at room temperature for 24 hours, the conversion into **368/369/370** was determined by analysis of the ¹H NMR spectra for the crude reaction mixture.

Result: No reaction observed.

Experimental procedure for exploring the potential of the hydroperoxide anion to act as an oxidant (Scheme 184)

To a vigorously stirring mixture of H₂O₂ (0.153 mL, 30% w/w aqueous solution, 1.5 mmol, 1.5 equiv.) and NaOH (0.060 g, 1.5 mmol, 1.5 equiv.) in toluene (3.5 mL) was added (*E*)-4-phenyl-3-buten-2-one (0.146 g, 1 mmol). The resulting mixture was stirred at room temperature for 2 hours. After this period, the standard work-up procedure was applied.

Result: No reaction observed.

General procedure 11: *Exploring the oxidation of 3,3-dimethyl-2-butanone (Scheme 185)*

To a vigorously stirring suspension of *m*CPBA (0.168 g, 0.75 mmol, 1.5 equiv.) in CDCl₃ or d₈-toluene (1.75 mL) as detailed was added DMAP (0.012 g, 0.1 mmol, 20 mol%) if specified and 3,3-dimethyl-2-butanone (0.062 mL, 0.5 mmol). The resulting mixture was stirred at room temperature for 2 hours. The reaction was then diluted with sufficient quantities of the appropriate deuterated solvent to ensure that all of the precipitate had dissolved and the mixture was homogenous. An aliquot of the reaction mixture was then removed for analysis by ¹H NMR spectroscopy. The conversion into ester **372** was determined by comparison of the integrals of the ^tBu signals of **371** and **372** at 1.14 ppm and 1.44 ppm in CDCl₃ and 0.86 ppm and 1.31 ppm in d₈-toluene respectively.

General procedure 12: *Examining the catalytic ability of N-oxides within the oxidation of acetophenone derivatives (Table 13)*

To a vigorously stirring suspension of *m*CPBA (0.336 g, 1.5 mmol, 1.5 equiv.) in toluene (3.5 mL) was added any specified catalyst (20 mol%) and the appropriate acetophenone derivative (1 mmol). The resulting mixture was stirred at room temperature for 2 hours, after which the standard work-up procedure was then applied.

General procedure 13: *Catalyst electronics study (Table 14)*

To an NMR tube containing a suspension of *m*CPBA (0.084 g, 0.375 mmol, 1.5 equiv.) in *d*₈-toluene (0.5 mL) was added the specified organocatalyst (20 mol%) rapidly followed by a solution of methoxybenzophenone (0.053 g, 0.25 mmol) in *d*₈-toluene (0.4 mL). The mixture was then left at room temperature for the specified period time; after which conversions were determined by analysis of the ¹H NMR spectra for the crude reaction mixture.

General procedure 14: *Epoxidation of (E)-stilbene (Scheme 187)*

To a vigorously stirring suspension of *m*CPBA (0.336 g, 1.5 mmol, 1.5 equiv.) in toluene (3.5 mL) was added DMAP (0.024 g, 0.2 mmol, 20 mol%) if specified and (*E*)-stilbene (0.180 g, 1 mmol). The resulting mixture was stirred at room temperature for 2 hours. The standard work-up procedure was then applied. Conversion into epoxide **388** was determined by analysis of the ¹H NMR spectra obtained in CDCl₃ for the crude reaction mixture. Specifically, this was achieved by comparing the integrals of the peaks at 3.89 ppm and 7.14 ppm attributable to epoxide **388** and (*E*)-stilbene **387** respectively.^{448,449}

General procedure 15: *Exploring the catalytic potential of sodium benzoates and other additives (Tables 27 and 28 and Scheme 222)*

To a vigorously stirring suspension of *m*CPBA (0.336 g, 1.5 mmol, 1.5 equiv.) in toluene (3.5 mL) was added any specified catalyst and/or additive followed by (*E*)-4-phenyl-3-buten-2-one (0.146 g, 1 mmol). The resulting mixture was stirred at room temperature for the specified period of time. The standard work-up procedure was then applied.

5.2.6 Procedures for examining the substrate generality**General procedure 16:** *Examining the substrate scope (Section 2.3.6 and Schemes 224, 228 and 233)*

To a vigorously stirring suspension of *m*CPBA in toluene (or CH₂Cl₂ where stated) was added if specified DMAP (0.024 g, 0.2 mmol, 20 mol%), followed by the appropriate ketone (1 mmol). The resulting mixture was stirred at room temperature for the specified period of time, after which the standard work-up procedure was then applied.

General procedure 17: *Enhanced temperature oxidations (Scheme 208)*

To a vigorously stirring suspension of *m*CPBA (0.336 g, 1.5 mmol, 1.5 equiv.) in toluene (3.5 mL) was added DMAP (0.024 g, 0.2 mmol, 20 mol%) where specified and the appropriate ketone

(1 mmol). The resulting mixture was stirred at room temperature or 50 °C for the specified period of time, after which the standard work-up procedure was then applied.

5.2.7 General procedures for vinyl ester synthesis

General Procedure 18a: *Synthesis of vinyl esters in the presence of DMAP*

To a vigorously stirring suspension of *m*CPBA (0.672 g, 3 mmol, 1.5 equiv.) in toluene (7 mL) was added DMAP (0.049 g, 0.4 mmol, 20 mol%) and the appropriate ketone (2 mmol). The resulting mixture was stirred at room temperature for the specified period of time, after which the standard work-up procedure was then applied. The crude product was purified by flash column chromatography, with the eluent as detailed, to afford the desired vinyl ester.

General Procedure 18b: *Synthesis of vinyl esters in the absence of DMAP*

General procedure **18a** was followed but in the absence of the DMAP catalyst.

5.2.8 General procedures for reactions of 3-(4-methoxyphenyl)but-3-en-2-one (485)

General procedure 19: *Mechanistic investigations for the oxidation and dimerisation reactions of 3-(4-methoxyphenyl)but-3-en-2-one (Scheme 227)*

To a stirring solution of 3-(4-methoxyphenyl)but-3-en-2-one (0.176 g, 1 mmol) in toluene (3.5 mL) was added benzoic acid (0.183 g, 1.5 mmol, 1.5 equiv.) and/or styrene oxide (0.114 mL, 1 mmol), as specified. The resulting mixture was stirred at room temperature for 2 hours. After this period, the standard work-up procedure was applied. Reaction progress was determined by analysis of the ¹H NMR spectra obtained in CDCl₃ for the crude reaction mixture.

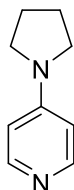
5.2.9 General procedures for the optimisation of by-products encountered

General procedure 20: *By-product optimisation (Section 2.3.10)*

To a vigorously stirring suspension of *m*CPBA in toluene was added if specified DMAP (10 mol%) and/or sodium bicarbonate (2.5 equiv.) followed by (*E*)-4-phenyl-3-buten-2-one or (*E*)-2-phenylethenyl acetate as detailed. The resulting mixture was stirred at room temperature for the specified period of time, after which the standard work-up procedure was then applied.

5.2.10 Experimental Data

4-(Pyrrolidin-1-yl)pyridine (361)

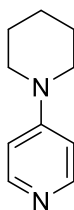


Pyrrolidine (0.417 mL, 5 mmol) was subjected to general procedure **1** to afford the title compound (0.340 g, 46%) as a pale brown, crystalline solid; **mp** 56-58 °C (lit. 57-58 °C).⁴²⁴

¹H NMR (300 MHz, CDCl₃): δ_{H} = 8.21-8.16 (2H, m, 2 x NCH), 6.39-6.33 (2H, m, 2 x NCHCH), 3.34-3.26 (4H, m, 2 x NCH₂), 2.07-1.97 (4H, m, 2 x NCH₂CH₂); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_{C} = 151.8, 149.6, 107.0, 47.0, 25.4; **IR** (neat): ν (cm⁻¹) = 3081, 3035, 2968, 2850 (C-H), 1593, 1516 (C-C, C-N pyridine); **HRMS** (ESI-TOF): m/z found 149.1097, C₉H₁₂N₂ [M+H]⁺ requires 149.1079.

Spectroscopic data was found to be consistent with that reported within the literature.⁴²⁴

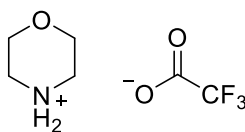
4-(Piperidin-1-yl)pyridine (362)



Piperidine (0.494 mL, 5 mmol) was subjected to general procedure **1** to afford the title compound (0.396 g, 49%) as a pale brown, crystalline solid; **mp** 79-81 °C (lit. 79-80 °C).^{424,721}

¹H NMR (300 MHz, CDCl₃): δ_{H} = 8.24-8.16 (2H, m, 2 x NCH), 6.65-6.58 (2H, m, 2 x NCHCH), 3.35-3.25 (4H, app. br. s, 2 x NCH₂), 1.67-1.57 (6H, app. br. s, 2 x NCH₂CH₂ and NCH₂CH₂CH₂); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_{C} = 155.0, 150.3, 108.3, 47.2, 25.2, 24.4; **IR** (neat): ν (cm⁻¹) = 3089, 3030, 2993, 2933, 2853 (C-H), 1592, 1508 (C-C, C-N pyridine); **HRMS** (ESI-TOF): m/z found 163.1239, C₁₀H₁₄N₂ [M+H]⁺ requires 163.1235.

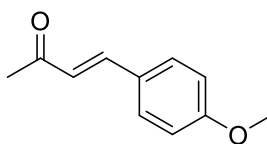
Spectroscopic data was found to be consistent with that reported within the literature.⁴²⁴

Morpholinium trifluoroacetate (389)

The following was based on a literature procedure published by List *et al.*⁴⁵⁰ To a stirring solution of morpholine (0.875 mL, 10 mmol) in Et₂O (20 mL) was added slowly a solution of trifluoroacetic acid (0.842 mL, 11 mmol) in Et₂O (10 mL) at 0 °C. Upon complete addition, the reaction mixture was stirred for 1 hour and then allowed to warm gradually to room temperature. The precipitate was filtered under nitrogen and washed sequentially with Et₂O and pentane to afford the title salt cleanly as a white solid.

¹H NMR (300 MHz, DMSO-d₆): δ_H = 9.50-8.90 (2H, br. s, NH₂), 3.79-3.72 (4H, m, 2 x OCH₂), 3.14-3.07 (4H, m, 2 x NH₂CH₂).

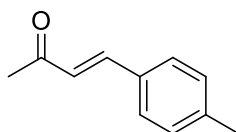
Spectroscopic data was found to be consistent with that reported within the literature.⁴⁵⁰

(3E)-4-(4-Methoxyphenyl)but-3-en-2-one (390)

p-Anisaldehyde (2.433 mL, 20 mmol) was subjected to general procedure **2b** and purification by flash column chromatography (eluent: petrol:EtOAc 90:10) afforded the title compound (3.053 g, 87%) as a pale yellow solid; **mp** 71-73 °C (lit. 72-74 °C).⁷²²

¹H NMR (300 MHz, CDCl₃): δ_H = 7.50 (2H, d, *J* = 8.7 Hz, 2 x CH₃OCCHCH), 7.48 (1H, d, *J* = 16.5 Hz, C(O)CH=CH), 6.92 (2H, d, *J* = 8.9 Hz, 2 x CH₃OCCH), 6.61 (1H, d, *J* = 16.2 Hz, C(O)CH=CH), 3.84 (3H, s, OCH₃), 2.36 (3H, s, C(O)CH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_C = 198.5, 161.8, 143.4, 130.1, 127.2, 125.2, 114.6, 55.5, 27.5; **IR** (neat): ν (cm⁻¹) = 1655 (C=O); **HRMS** (ESI-TOF): *m/z* found 177.0925, C₁₁H₁₂O₂ [M+H]⁺ requires 177.0916.

Spectroscopic data was found to be consistent with that reported within the literature.⁷²³

(3E)-4-(4-Methylphenyl)but-3-en-2-one (391)

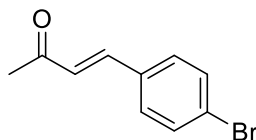
p-Tolualdehyde (4.716 mL, 40 mmol) was subjected to general procedure **2b** but on double the scale detailed within the method. The crude product was purified by Kugelrohr distillation under

reduced pressure to afford the title compound (4.291 g, 67%) as a cream, waxy solid; **mp** 30-31 °C (lit. 31 °C).⁷²⁴

¹H NMR (300 MHz, CDCl₃): δ_{H} = 7.48 (1H, d, J = 16.4 Hz, C(O)CH=CH), 7.42 (2H, d, J = 8.2 Hz, 2 x CH=CHCCH), 7.19 (2H, d, J = 8.0 Hz, 2 x CH=CHCCHCH), 6.66 (1H, d, J = 16.3 Hz, C(O)CH=CH), 2.36 (3H, s, CH₃), 2.35 (3H, s, CH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_{C} = 198.5, 143.6, 141.1, 131.7, 129.8, 128.3, 126.3, 27.5, 21.5; **IR** (neat): ν (cm⁻¹) = 1656 (C=O), 1604 (C=C alkene); **HRMS** (ESI-TOF): m/z found 161.0971, C₁₁H₁₂O [M+H]⁺ requires 161.0966.

Spectroscopic data was found to be consistent with that reported within the literature.⁷²³

(3E)-4-(4-Bromophenyl)but-3-en-2-one (392)

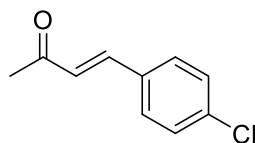


The following was based on a literature procedure published by Zhu *et al.*⁷²⁵ To a stirring solution of 4-bromobenzaldehyde (5.551 g, 30 mmol) in acetone (30 mL) and EtOH (3 mL) was added slowly 10% aqueous NaOH solution (24 mL) at 0 °C. Upon complete addition, H₂O (120 mL) was added and the reaction mixture was then allowed to warm to room temperature before being stirred for 24 hours. The precipitate was collected by vacuum filtration and the cake was washed with water and then air dried. The crude product was purified by Kugelrohr distillation to afford the title compound (3.636 g, 54%) as a white, crystalline solid; **mp** 84-85 °C (lit. 83-84 °C).⁷²²

¹H NMR (250 MHz, CDCl₃): δ_{H} = 7.54 (2H, d, J = 8.6 Hz, 2 x BrCCH), 7.44 (1H, d, J = 16.0 Hz, C(O)CH=CH), 7.41 (2H, d, J = 8.5, 2 x BrCCHCH), 6.70 (1H, d, J = 16.3 Hz, C(O)CH=CH), 2.38 (3H, s, CH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_{C} = 198.2, 142.1, 133.5, 132.4, 129.7, 127.7, 124.9, 27.8; **IR** (neat): ν (cm⁻¹) = 1655 (C=O); **HRMS** (ESI-TOF): m/z found 246.9708, C₁₀H₉OBr [M+Na]⁺ requires 246.9734.

Spectroscopic data was found to be consistent with that reported within the literature.⁷²⁶

(3E)-4-(4-Chlorophenyl)but-3-en-2-one (393)



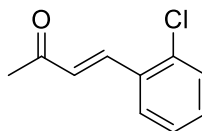
The following was based on a literature procedure published by Zhu *et al.*⁷²⁵ To a stirring solution of 4-chlorobenzaldehyde (8.434 g, 60 mmol) in acetone (60 mL) and EtOH (6 mL) was added

slowly 10% aqueous NaOH solution (48 mL) at 0 °C. Upon complete addition, H₂O (240 mL) was added and the reaction mixture was then allowed to warm to room temperature before being stirred for 24 hours. The precipitate was collected by vacuum filtration and the cake was washed with H₂O and then air dried to afford the title compound (10.063 g, 93%) cleanly as an off-white solid; **mp** 56-58 °C (lit. 56-57 °C).⁷²⁵

¹H NMR (250 MHz, CDCl₃): δ_H = 7.52-7.42 (3H, m, C(O)CH=CH and 2 x ArH), 7.41-7.34 (2H, m, ArH), 6.69 (1H, d, J = 16.3 Hz, C(O)CH=CH), 2.38 (3H, s, CH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_C = 198.1, 141.9, 136.5, 133.0, 129.5, 129.3, 127.6, 27.8; **IR** (neat): ν (cm⁻¹) = 1656 (C=O), 1609 (C=C alkene); **HRMS** (ESI-TOF): m/z found 203.0232, C₁₀H₉OCl [M+Na]⁺ requires 203.0240.

Spectroscopic data was found to be consistent with that reported within the literature.⁷²³

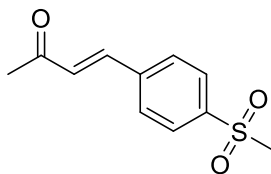
(3E)-4-(2-Chlorophenyl)but-3-en-2-one (394)



The following was based on a literature procedure published by Zhu *et al.*⁷²⁵ To a stirring solution of 2-chlorobenzaldehyde (3.398 mL, 30 mmol) in acetone (30 mL) and EtOH (3 mL) was added slowly 10% aqueous NaOH solution (24 mL) at 0 °C. Upon complete addition, H₂O (120 mL) was added and the reaction mixture was then allowed to warm to room temperature before being stirred for 24 hours. The acetone was then removed *in vacuo* and the mixture was extracted with EtOAc (2 x 120 mL). The combined organic phases were dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (eluent: petrol:EtOAc 90:10) to afford the title compound (3.922 g, 72%) as a yellow oil.

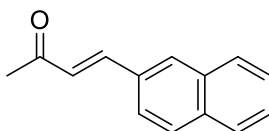
¹H NMR (300 MHz, CDCl₃): δ_H = 7.93 (1H, d, J = 16.3 Hz, C(O)CH=CH), 7.64 (1H, dd, J = 6.9, 2.1 Hz, ArH), 7.46-7.40 (1H, m, ArH), 7.37-7.24 (2H, m, ArH), 6.66 (1H, d, J = 16.4 Hz, C(O)CH=CH), 2.42 (3H, s, CH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_C = 198.5, 139.4, 135.2, 132.8, 131.4, 130.3, 129.8, 127.7, 127.3, 27.4; **IR** (neat): ν (cm⁻¹) = 1670 (C=O), 1608 (C=C alkene); **HRMS** (ESI-TOF): m/z found 181.0416, C₁₀H₉OCl [M+H]⁺ requires 181.0420.

Spectroscopic data was found to be consistent with that reported within the literature.^{727,728}

(3E)-4-(4-Methanesulfonylphenyl)but-3-en-2-one (395)

The following was based on a literature procedure published by Zhu *et al.*⁷²⁵ To a stirring solution of 4-(methylsulfonyl)benzaldehyde (11.053 g, 60 mmol) in acetone (60 mL) and EtOH (6 mL) was added slowly 10% aqueous NaOH solution (48 mL) at 0 °C. Upon complete addition, H₂O (240 mL) was added and the reaction mixture was then allowed to warm to room temperature before being stirred for 24 hours. The acetone was then removed *in vacuo* and the mixture was extracted with EtOAc (2 x 240 mL). The combined organic phases were dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (petrol:EtOAc 60:40 → 50:50) to afford the title compound (1.120 g, 8%) as a white solid; **mp** 183-185 °C (lit. 124-125 °C).⁷²⁹

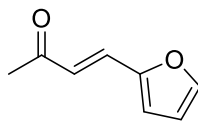
¹H NMR (300 MHz, CDCl₃): δ_H = 7.90 (2H, d, *J* = 8.4 Hz, 2 x S(O)₂CCH), 7.67 (2H, d, *J* = 8.3 Hz, 2 x S(O)₂CCHCH), 7.47 (1H, d, *J* = 16.3 Hz, C(O)CH=CH), 6.75 (1H, d, *J* = 16.3 Hz, C(O)CH=CH), 3.03 (3H, s, S(O)₂CH₃), 2.35 (3H, s, C(O)CH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_C = 197.8, 141.5, 140.5, 139.7, 130.0, 128.8, 127.9, 44.3, 27.9; **IR** (neat): ν (cm⁻¹) = 1669 (C=O); **HRMS** (ESI-TOF): *m/z* found 247.0398, C₁₁H₁₂O₃S [M+Na]⁺ requires 247.0405.

(3E)-4-(Naphthalen-2-yl)but-3-en-2-one (396)

2-Napthaldehyde (4.685 g, 30 mmol) was subjected to general procedure **2a**. The crude product was passed through a silica plug (eluent: pentane:EtOAc 95:5) to afford the title compound (5.237 g, 89%) as a white solid; **mp** 99-100 °C (lit. 103-104 °C).⁷³⁰

¹H NMR (300 MHz, CDCl₃): δ_H = 7.98-7.94 (1H, app. br. s, ArH), 7.89-7.81 (3H, m, ArH), 7.68 (1H, d, *J* = 16.2 Hz, C(O)CH=CH), 7.68 (1H, dd, *J* = 8.7, 1.7 Hz, ArH), 7.57-7.49 (2H, m, ArH), 6.84 (1H, d, *J* = 16.3 Hz, C(O)CH=CH), 2.43 (3H, s, CH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_C = 198.5, 143.7, 134.5, 133.4, 132.1, 130.5, 128.9, 128.7, 127.9, 127.5, 127.4, 126.9, 123.6, 27.8; **IR** (neat): ν (cm⁻¹) = 1665 (C=O), 1618 (C=C alkene); **HRMS** (ESI-TOF): *m/z* found 197.0967, C₁₄H₁₂O [M+H]⁺ requires 197.0966.

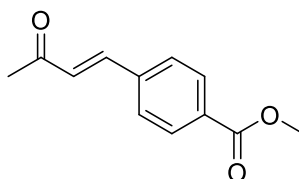
Spectroscopic data was found to be consistent with that reported within the literature.⁷³¹

(3E)-4-(Furan-2-yl)but-3-en-2-one (397)

Furfural (2.485 mL, 30 mmol) was subjected to general procedure **2a** and purification by flash column chromatography (eluent: pentane:EtOAc 90:10) afforded the title compound (3.128 g, 77%) as a colourless oil.

¹H NMR (300 MHz, CDCl₃): δ_{H} = 7.48 (1H, d, J = 1.6 Hz, OCH), 7.26 (1H, d, J = 16.0 Hz, C(O)CH=CH), 6.65 (1H, d, J = 3.4 Hz, OCHCHCH), 6.59 (1H, d, J = 15.9 Hz, C(O)CH=CH), 6.47 (1H, dd, J = 3.4, 1.8 Hz, OCHCH), 2.30 (3H, s, CH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_{C} = 197.9, 150.9, 145.1, 129.5, 124.4, 115.8, 112.6, 27.9; **IR** (neat): ν (cm⁻¹) = 1656 (C=O), 1622 (C=C alkene); **HRMS** (ESI-TOF): m/z found 137.0611, C₈H₈O₂ [M+H]⁺ requires 137.0603.

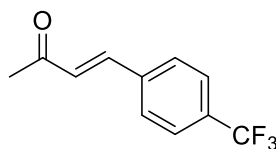
Spectroscopic data was found to be consistent with that reported within the literature.⁷³²

Methyl 4-[(1E)-3-oxobut-1-en-1-yl]benzoate (398)

Methyl 4-formylbenzoate (4.925 g, 30 mmol) was subjected to general procedure **2a** and purification by flash column chromatography (eluent: Pentane:EtOAc 80:20) afforded the title compound (2.619 g, 43%) as a white solid; **mp** 115-116 °C (lit. 102 °C).⁷²⁴

¹H NMR (300 MHz, CDCl₃): δ_{H} = 8.06 (2H, d, J = 8.4 Hz, 2 x OC(O)CCH), 7.60 (2H, d, J = 8.3 Hz, 2 x OC(O)CCHCH), 7.52 (1H, d, J = 16.3 Hz, C(O)CH=CH), 6.78 (1H, d, J = 16.3 Hz, C(O)CH=CH), 3.93 (3H, s, OCH₃), 2.40 (3H, s, C(O)CH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_{C} = 198.2, 166.5, 142.0, 138.8, 131.7, 130.3, 129.1, 128.2, 52.5, 27.9; **IR** (neat): ν (cm⁻¹) = 1720 (C=O ester), 1662 (C=O ketone); **HRMS** (ESI-TOF): m/z found 205.0863, C₁₂H₁₂O₃ [M+H]⁺ requires 205.0865.

Spectroscopic data was found to be consistent with that reported within the literature.⁷³¹

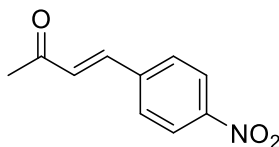
(3E)-4-[4-(Trifluoromethyl)phenyl]but-3-en-2-one (399)

4-(Trifluoromethyl)benzaldehyde (4.097 mL, 30 mmol) was subjected to general procedure **2a**. The crude product was passed through a silica plug (eluent: pentane:EtOAc 95:5) to afford the title compound (6.079 g, 95%) as a colourless oil.

¹H NMR (250 MHz, CDCl₃): δ_{H} = 7.63 (4H, app. s, ArH), 7.51 (1H, d, J = 16.3 Hz, C(O)CH=CH), 6.76 (1H, d, J = 16.3 Hz, C(O)CH=CH), 2.39 (3H, s, CH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_{C} = 198.0, 141.4, 138.0 (app. d, $^4J_{\text{CF}}$ = 1.3 Hz), 132.0 (q, $^2J_{\text{CF}}$ = 32.7 Hz), 129.2, 128.5, 126.0 (q, $^3J_{\text{CF}}$ = 3.8 Hz), 123.9 (q, $^1J_{\text{CF}}$ = 272.2 Hz), 27.9; **IR** (neat): ν (cm⁻¹) = 1689, 1663 (C=O), 1615 (C=C alkene); **HRMS** (ESI-TOF): m/z found 237.0517, C₁₁H₉F₃O [M+Na]⁺ requires 237.0503.

Spectroscopic data was found to be consistent with that reported within the literature.⁷²³

(3E)-4-(4-Nitrophenyl)but-3-en-2-one (400)

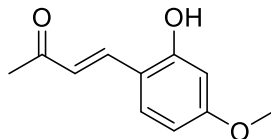


4-Nitrobenzaldehyde (4.534 g, 30 mmol) was subjected to general procedure **2a** and purification by flash column chromatography (eluent: pentane:EtOAc 80:20) afforded the title compound (3.792 g, 66%) as a white solid; **mp** 107-109 °C (lit. 107-109 °C).⁷³³

¹H NMR (300 MHz, CDCl₃): δ_{H} = 8.23 (2H, d, J = 8.8 Hz, 2 x CHCNO₂), 7.68 (2H, d, J = 8.8 Hz, 2 x CHCHCNO₂), 7.52 (1H, d, J = 16.3 Hz, C(O)CH=CH), 6.80 (1H, d, J = 16.3 Hz, C(O)CH=CH), 2.41 (3H, s, CH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_{C} = 197.7, 148.6, 140.8, 140.2, 130.5, 128.9, 124.3, 28.1; **IR** (neat): ν (cm⁻¹) = 1691, 1668 (C=O), 1615, 1593 (C=C alkene), 1508 (N-O), 1333 (N-O); **HRMS** (ESI-TOF): m/z found 192.0665, C₁₀H₉NO₃ [M+H]⁺ requires 192.0661.

Spectroscopic data was found to be consistent with that reported within the literature.⁷³¹

(3E)-4-(2-Hydroxy-4-methoxyphenyl)but-3-en-2-one (401)

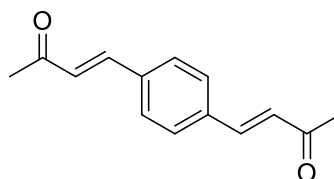


2-Hydroxy-4-methoxybenzaldehyde (4.565 g, 30 mmol) was subjected to general procedure **2a** and purification by flash column chromatography (eluent: pentane:Et₂O 25:75) afforded the title compound (1.227 g, 21%) as a yellow solid; **mp** 128-130 °C (lit. 129-130 °C).⁷³⁴

¹H NMR (300 MHz, CDCl₃): δ_{H} = 8.34-8.28 (1H, br. s, OH), 7.79 (1H, d, J = 16.3 Hz, C(O)CH=CH), 7.37 (1H, d, J = 8.6 Hz, CHCHCCHCOH), 7.03 (1H, d, J = 16.3 Hz, C(O)CH=CH), 6.51 (1H, d, J = 2.3 Hz, CHCOH), 6.48 (1H, dd, J = 8.5, 2.4 Hz, CHCCHCOH), 3.80 (3H, s, OCH₃), 2.41 (3H, s, C(O)CH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_{C} = 201.8, 163.2, 158.4, 141.9, 131.7, 125.4, 114.8, 107.3, 101.9, 55.6, 26.7; **IR** (neat): ν (cm⁻¹) = 3154 (O-H) 1667 (C=O); **HRMS** (ESI-TOF): m/z found 215.0682, C₁₁H₁₂O₃ [M+Na]⁺ requires 215.0684.

Spectroscopic data was found to be consistent with that reported within the literature.⁷³⁴

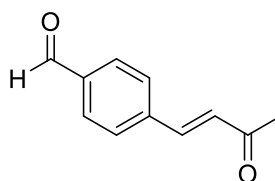
(3E)-4-{4-[(1E)-3-Oxobut-1-en-1-yl]phenyl}but-3-en-2-one (402)



Terephthalaldehyde (4.024 g, 30 mmol) was subjected to general procedure **2a** and purification by flash column chromatography (eluent: pentane:EtOAc 95:5) afforded the title compound (4.032 g, 63%) as a white solid; **mp** 150-152 °C (lit. 159 °C).⁷³⁵

¹H NMR (250 MHz, CDCl₃): δ_{H} = 7.56 (4H, s, ArH), 7.49 (2H, d, J = 16.2 Hz, 2 x C(O)CH=CH), 6.74 (2H, d, J = 16.2 Hz, 2 x C(O)CH=CH), 2.39 (6H, s, 2 x CH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_{C} = 198.3, 142.2, 136.5, 128.9, 128.1, 27.9; **IR** (neat): ν (cm⁻¹) = 1662 (C=O), 1620 (C=C alkene); **HRMS** (ESI-TOF): m/z found 215.1067, C₁₄H₁₄O₂ [M+H]⁺ requires 215.1072.

4-[(1E)-3-Oxobut-1-en-1-yl]benzaldehyde (410)

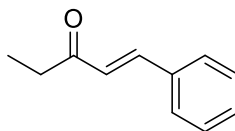


Terephthalaldehyde (4.024 g, 30 mmol) was subjected to general procedure **2a** and purification by flash column chromatography (eluent: pentane:EtOAc 95:5) afforded the title compound (0.662 g, 13%) as a white solid; **mp** 68-69 °C.

¹H NMR (300 MHz, CDCl₃): δ_{H} = 10.03 (1H, s, C(O)H), 7.91 (2H, d, J = 8.3 Hz, 2 x CHCC(O)H), 7.69 (2H, d, J = 8.2 Hz, 2 x CHCHCC(O)H), 7.53 (1H, d, J = 16.3 Hz, C(O)CH=CH), 6.81 (1H, d, J = 16.3 Hz, C(O)CH=CH), 2.41 (3H, s, CH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_{C} = 198.0, 191.5, 141.5, 140.3, 137.4, 130.3, 129.7, 128.8, 28.0; **IR** (neat): ν (cm⁻¹) = 1686 (C=O aldehyde), 1661 (C=O ketone), 1611, 1602 (C=C alkene); **HRMS** (ESI-TOF): m/z found 175.0770, C₁₁H₁₀O₂ [M+H]⁺ requires 175.0759.

Spectroscopic data was found to be consistent with that reported within the literature.⁷³¹

(1E)-1-Phenylpent-1-en-3-one (403)

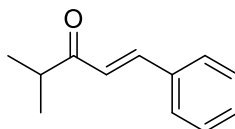


2-Butanone (2.687 mL, 30 mmol) and benzaldehyde (3.049 mL, 30 mmol) were subjected to a modified version of general procedure **2a** in the absence of acetone and purification by flash column chromatography (eluent: pentane:EtOAc 95:5) afforded the title compound (2.678 g, 56%) as a white solid; **mp** 36-38 °C (lit. 36-38 °C).⁷³⁶

¹H NMR (250 MHz, CDCl₃): δ_H = 7.56 (1H, d, J = 16.0 Hz, C(O)CH=CH), 7.58-7.50 (2H, m, PhH), 7.43-7.35 (3H, m, PhH), 6.75 (1H, d, J = 16.2 Hz, C(O)CH=CH), 2.70 (2H, q, J = 7.3 Hz, CH₂), 1.17 (3H, t, J = 7.3 Hz, CH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_C = 201.1, 142.3, 134.7, 130.5, 129.4, 128.3, 126.1, 34.2, 8.4; **IR** (neat): ν (cm⁻¹) = 1691, 1666 (C=O), 1614, 1594 (C=C alkene); **HRMS** (ESI-TOF): m/z found 183.0790, C₁₁H₁₂O [M+Na]⁺ requires 183.0786.

Spectroscopic data was found to be consistent with that reported within the literature.⁷³⁷

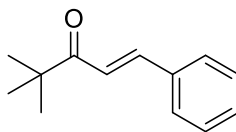
(1E)-4-Methyl-1-phenylpent-1-en-3-one (404)



3-Methyl-2-butanone (3.210 mL, 30 mmol) and benzaldehyde (3.049 mL, 30 mmol) were subjected to a modified version of general procedure **2a** in the absence of acetone and purification by flash column chromatography (eluent: pentane:EtOAc 95:5) afforded the title compound (1.976 g, 38%) as a yellow oil.

¹H NMR (250 MHz, CDCl₃): δ_H = 7.60 (1H, d, J = 16.1 Hz, C(O)CH=CH), 7.59-7.50 (2H, m, PhH), 7.43-7.32 (3H, m, PhH), 6.81 (1H, d, J = 16.1 Hz, C(O)CH=CH), 2.92 (1H, sept., J = 6.9 Hz, CH₃CH), 1.17 (6H, d, J = 6.9 Hz, 2 x CH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_C = 203.8, 142.4, 134.7, 130.4, 128.9, 128.3, 124.5, 39.3, 18.5; **IR** (neat): ν (cm⁻¹) = 1687, 1662 (C=O), 1611 (C=C alkene); **HRMS** (ESI-TOF): m/z found 175.1122, C₁₂H₁₄O [M+H]⁺ requires 175.1123.

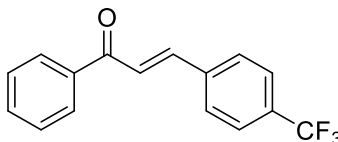
Spectroscopic data was found to be consistent with that reported within the literature.⁷³⁸

(1E)-4,4-Dimethyl-1-phenylpent-1-en-3-one (405)

The following was based on a modified version of general procedure **2b**. To a stirring solution of benzaldehyde (2.297 mL, 22.6 mmol) and 3,3-dimethyl-2-butanone (2.501 mL, 20 mmol) in EtOH (10 mL) was added 10% aqueous NaOH solution (0.565 mL) dropwise over 30 minutes at 0 °C. The reaction and work-up conditions specified in general procedure **2b** were then followed. The crude product was purified by flash column chromatography (eluent: petrol:EtOAc 95:5) to afford the title compound (1.471 g, 39%) as an off-white, waxy solid; **mp** 38-40 °C (lit. 38-40 °C).⁷³⁹

¹H NMR (300 MHz, CDCl₃): δ_{H} = 7.69 (1H, d, J = 15.6 Hz, C(O)CH=CH), 7.61-7.54 (2H, m, PhH), 7.42-7.35 (3H, m, PhH), 7.13 (1H, d, J = 15.6 Hz, C(O)CH=CH), 1.23 (9H, s, 3 x CH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_{C} = 204.4, 143.0, 135.1, 130.3, 129.0, 128.4, 120.9, 43.4, 26.5; **IR** (neat): ν (cm⁻¹) = 1681 (C=O), 1611 (C=C alkene); **HRMS** (ESI-TOF): m/z found 211.1101, C₁₃H₁₆O [M+Na]⁺ requires 211.1099.

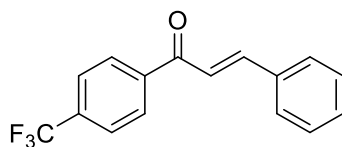
Spectroscopic data was found to be consistent with that reported within the literature.⁷²³

(2E)-1-Phenyl-3-[4-(trifluoromethyl)phenyl]prop-2-en-1-one (406)

4-(Trifluoromethyl)benzaldehyde (2.731 mL, 20 mmol) was reacted with acetophenone (2.333 mL, 20 mmol) according to general procedure **2c**. Recrystallisation of the collected solid from EtOH afforded the title compound (3.911 g, 71%) as a yellow, crystalline solid; **mp** 128-130 °C (lit. 128-129 °C).⁷⁴⁰

¹H NMR (300 MHz, CDCl₃): δ_{H} = 8.06-8.00 (2H, m, PhH), 7.81 (1H, d, J = 15.8 Hz, C(O)CH=CH), 7.73 (2H, d, J = 8.3 Hz, 2 x CF₃CCH), 7.66 (2H, d, J = 8.4 Hz, 2 x CF₃CCHCH), 7.60 (1H, d, J = 15.6 Hz, C(O)CH=CH), 7.61-7.57 (1H, m, PhH), 7.55-7.48 (2H, m, PhH); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_{C} = 190.1, 142.8, 138.4 (app. d, $^4J_{\text{CF}}$ = 1.4 Hz), 137.9, 133.3, 132.0 (q, $^2J_{\text{CF}}$ = 32.5 Hz), 128.9, 128.7, 128.6, 126.0 (q, $^3J_{\text{CF}}$ = 3.8 Hz), 124.3, 124.0 (q, $^1J_{\text{CF}}$ = 272.3 Hz); **IR** (neat): ν (cm⁻¹) = 1663 (C=O), 1609 (C=C alkene); **HRMS** (ESI-TOF): m/z found 299.0654, C₁₆H₁₁OF₃ [M+Na]⁺ requires 299.0660.

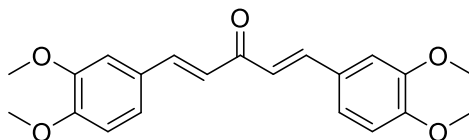
Spectroscopic data was found to be consistent with that reported within the literature.⁷⁴¹

(2E)-3-Phenyl-1-[4-(trifluoromethyl)phenyl]prop-2-en-1-one (407)

Benzaldehyde (2.031 mL, 20 mmol) was reacted with 4'-(trifluoromethyl)acetophenone (3.763 g, 20 mmol) according to general procedure **2c**. The crude product was purified by flash column chromatography (eluent: pentane:EtOAc 90:10) to afford the title compound (3.142 g, 57%) as a yellow, crystalline solid; **mp** 122-124 °C (lit. 117.5-118.5 °C).⁷⁴²

¹H NMR (300 MHz, CDCl₃): δ_{H} = 8.11 (2H, d, J = 8.1 Hz, 2 x CF₃CCH), 7.84 (1H, d, J = 15.7, C(O)CH=CH), 7.77 (2H, d, J = 8.2 Hz, 2 x CF₃CCHCH), 7.69-7.62 (2H, m, PhH), 7.50 (1H, d, J = 15.8 Hz, C(O)CH=CH), 7.46-7.41 (3H, m, PhH); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_{C} = 189.8, 146.3, 141.2, 134.6, 134.1 (app. d, $^2J_{\text{CF}}$ = 32.8 Hz), 131.1, 129.2, 128.9, 128.8, 125.8 (q, $^3J_{\text{CF}}$ = 3.7 Hz), 123.8 (app. d, $^1J_{\text{CF}}$ = 272.6 Hz), 121.7; **IR** (neat): ν (cm⁻¹) = 1665 (C=O), 1601 (C=C alkene); **HRMS** (ESI-TOF): m/z found 299.0641, C₁₆H₁₁F₃O [M+Na]⁺ requires 299.0660.

Spectroscopic data was found to be consistent with that reported within the literature.⁷⁴¹

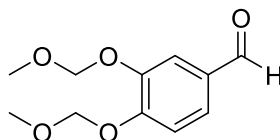
(1E,4E)-1,5-Bis(3,4-dimethoxyphenyl)penta-1,4-dien-3-one (408)

The following was based on a literature procedure published by Aher *et al.*⁷⁴³ To a stirring solution of EtOH (15 mL) and 10% aqueous NaOH solution (15 mL) was added acetone (1.101 mL, 15 mmol) in a single portion followed by 3,4-dimethoxybenzaldehyde (4.985 g, 30 mmol) portionwise at 0 °C. The resulting mixture was then allowed to warm gradually to room temperature and was stirred for a further 4 hours. The precipitate was collected by vacuum filtration and the cake was washed with water and then air dried. The collected solid was then recrystallised from EtOH, with any residual solvent removed using a high-vacuum line, to afford the title compound (3.928 g, 74%) as a bright yellow solid; **mp** 70-71 °C (lit. 72-75 °C).⁷⁴⁴

¹H NMR (250 MHz, CDCl₃): δ_{H} = 7.69 (2H, d, J = 15.9 Hz, 2 x C(O)CH=CH), 7.20 (2H, dd, J = 8.3, 1.7 Hz, 2 x CH₃OCCHCH), 7.14 (2H, d, J = 1.7 Hz, 2 x CH₃OCCHC), 6.95 (2H, d, J = 15.9 Hz, 2 x C(O)CH=CH), 6.89 (2H, d, J = 8.3 Hz, 2 x CH₃OCCHCH), 3.94 (6H, s, 2 x CH₃), 3.92 (6H, s, 2 x CH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_{C} = 188.8, 151.4, 149.3, 143.2, 127.9, 123.7, 123.3, 111.2, 109.9, 56.1, 56.0; **IR** (neat): ν (cm⁻¹) = 1646 (C=O); **HRMS** (ESI-TOF): m/z found 355.1552, C₂₁H₂₂O₅ [M+H]⁺ requires 355.1545.

Spectroscopic data was found to be consistent with that reported within the literature.⁷⁴⁵

3,4-Bis(methoxymethoxy)benzaldehyde (412)

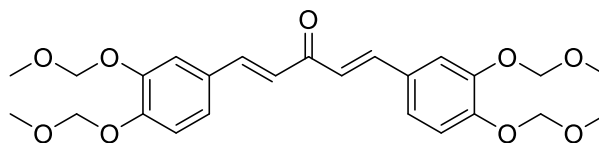


The following was based on a literature procedure published by Busqué, Ruiz-Molina and co-workers.⁴⁵¹ To a stirring solution of 3,4-dihydroxybenzaldehyde (0.497 g, 3.6 mmol) in CH₂Cl₂ (5 mL) was added ⁱPr₂EtN (3.762 mL, 21.6 mmol) and DMAP (0.050 g, 0.41 mmol) at 0 °C. Bromomethyl methyl ether (1.306 mL, 90% purity, 14.4 mmol) was then added dropwise and the resulting mixture was stirred for a further hour at 0 °C. The mixture was then warmed to room temperature before being heated under reflux for 24 hours. After allowing the reaction mixture to cool to room temperature, brine (7.5 mL) was added and the resulting phases were separated. The aqueous phase was extracted three times with CHCl₃ (3 x 3.5 mL) and the combined organic phases were dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (hexane:EtOAc 90:10) to afford the title compound (0.748 g, 92%) as a pale yellow oil.

¹H NMR (250 MHz, CDCl₃): δ_H = 9.81 (1H, s, C(O)H), 7.63 (1H, d, *J* = 1.8 Hz, OCCHC), 7.46 (1H, dd, *J* = 8.3, 1.8 Hz, OCCHCH), 7.23 (1H, d, *J* = 8.3 Hz, OCCHCH), 5.28 (2H, s, CH₂), 5.25 (2H, s, CH₂), 3.48 (3H, s, CH₃), 3.47 (3H, s, CH₃).

Spectroscopic data was found to be consistent with that reported within the literature.⁷⁴⁶

(1E,4E)-1,5-Bis[3,4-bis(methoxymethoxy)phenyl]penta-1,4-dien-3-one (409)

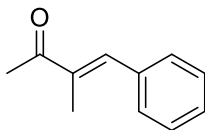


The following was based on a literature procedure published by Aher *et al.*⁷⁴³ To a stirring solution of EtOH (0.75 mL) and 10% aqueous NaOH solution (0.75 mL) was added a mixture of 3,4-bis(methoxymethoxy)benzaldehyde (0.339 g, 1.5 mmol) and acetone (0.055 mL, 0.75 mmol) portionwise in order to maintain the temperature between 20 and 25 °C. Upon complete addition, the resulting mixture was stirred for a further 24 hours. The precipitate was collected by vacuum filtration, washed with H₂O and then air dried. Recrystallisation of the collected solid from EtOH afforded the title compound (0.216 g, 30%) as a yellow solid; **mp** 99-100 °C (lit. 100-101 °C).⁷⁴⁷

¹H NMR (250 MHz, CDCl₃): δ_{H} = 7.67 (2H, d, J = 15.9 Hz, 2 x C(O)CH=CH), 7.46 (2H, d, J = 1.7 Hz, 2 x OCCHC), 7.28-7.22 (2H, m, 2 x OCCHCH), 7.19 (2H, d, J = 8.4 Hz, 2 x OCCHCH), 6.96 (2H, d, J = 15.9 Hz, 2 x C(O)CH=CH), 5.30 (4H, s, 2 x CH₂), 5.29 (4H, s, 2 x CH₂), 3.56 (6H, s, 2 x CH₃), 3.53 (6H, s, 2 x CH₃).

Spectroscopic data was found to be consistent with that reported within the literature.⁷⁴⁸

(3E)-3-Methyl-4-phenylbut-3-en-2-one (413)

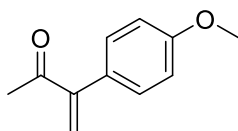


The following was based on a literature procedure published by Moran *et al.*⁴⁵² To a stirring mixture of glacial acetic acid (30 mL), benzaldehyde (3.047 mL, 30 mmol) and 2-butanone (5.375 mL, 60 mmol) was added H₂SO₄ (6 mL) dropwise. Upon complete addition, the reaction mixture was stirred at room temperature for a further 24 hours. Sufficient quantities of 10% aqueous NaOH solution were then added to neutralise the reaction, after which the mixture was extracted with three successive portions of Et₂O. The combined organic phases were washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (eluent: pentane:EtOAc 95:5) to afford the title compound (1.261 g, 26%) as a colourless oil.

¹H NMR (250 MHz, CDCl₃): δ_{H} = 7.52 (1H, d, J = 1.3 Hz, C(O)C=CH), 7.45-7.29 (5H, m, PhH), 2.46 (3H, s, C(O)CH₃), 2.06 (3H, d, J = 1.4 Hz, CH=CCH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_{C} = 200.4, 139.8, 137.8, 136.0, 129.8, 128.6, 128.5, 25.9, 13.0; **IR** (neat): ν (cm⁻¹) = 1687, 1662 (C=O), 1611, 1603 (C=C alkene); **HRMS** (ESI-TOF): m/z found 183.0787, C₁₁H₁₂O [M+Na]⁺ requires 183.0786.

Spectroscopic data was found to be consistent with that reported within the literature.^{452,749}

3-(4-Methoxyphenyl)but-3-en-2-one (485)



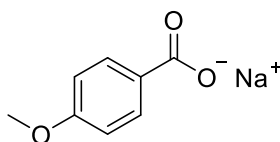
The following was based on a literature procedure published by Moran *et al.*⁴⁷⁴ To a stirring solution of 4-methoxyphenylacetone (15.389 mL, 100 mmol) in glacial acetic acid (90 mL) was added sequentially aqueous formaldehyde (24 mL, 37% w/w solution, 322 mmol) and morpholine (3 drops). The resulting mixture was then heated under reflux for 24 hours. After allowing the

reaction mixture to cool to room temperature, sufficient quantities of aqueous NaOH (0.1 M) were added to neutralise the solution. The reaction mixture was then extracted three times with EtOAc and the combined organic phases were washed sequentially with 10% aqueous NaHCO₃ solution and brine, before being dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (eluent: pentane:EtOAc 90:10) to afford the title compound (0.746 g, 42%) as a colourless oil.

¹H NMR (300 MHz, CDCl₃): δ_{H} = 7.26 (2H, d, J = 8.9 Hz, 2 x OCCHCH), 6.89 (2H, d, J = 8.9 Hz, 2 x OCCH), 6.09 (1H, app. s, CH_AH_B), 5.93 (1H, app. s, CH_AH_B), 3.81 (3H, s, OCH₃), 2.44 (3H, s, C(O)CH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_{C} = 200.0, 159.7, 149.0, 129.8, 129.4, 124.8, 113.7, 55.4, 27.6; **IR** (neat): ν (cm⁻¹) = 1666 (C=O); **HRMS** (ESI-TOF): m/z found 199.0734, C₁₁H₁₂O₂ [M+Na]⁺ requires 199.0735.

Spectroscopic data was found to be consistent with that reported within the literature.⁴⁷⁶

Sodium 4-methoxybenzoate (479)

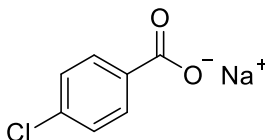


4-Methoxybenzoic acid (0.609 g, 4 mmol) was subjected to general procedure **3** to afford the title salt cleanly as a beige solid.

¹H NMR (250 MHz, DMSO-*d*₆): δ_{H} = 7.82 (2H, d, J = 8.8 Hz, 2 x C(O)CCH), 6.80 (2H, d, J = 8.8 Hz, 2 x OCCH), 3.74 (3H, s, CH₃); **IR** (neat): ν (cm⁻¹) = 1541, 1408 (COO⁻).

IR spectroscopic data was found to be consistent with that reported within the literature.⁷⁵⁰

Sodium 4-chlorobenzoate (480)

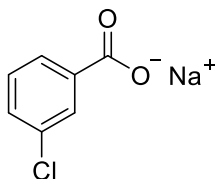


4-Chlorobenzoic acid (0.626 g, 4 mmol) was subjected to general procedure **3** to afford the title salt cleanly as a white solid.

¹H NMR (300 MHz, DMSO-*d*₆): δ_{H} = 7.87 (2H, d, J = 8.6 Hz, 2 x C(O)CCH), 7.31 (2H, d, J = 8.5 Hz, 2 x ClCCH); **IR** (neat): ν (cm⁻¹) = 1538, 1392 (COO⁻).

IR spectroscopic data was found to be consistent with that reported within the literature.^{751,752}

Sodium 3-chlorobenzoate (481)

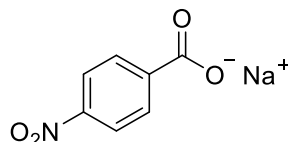


3-Chlorobenzoic acid (0.626 g, 4 mmol) was subjected to general procedure **3** to afford the title salt cleanly as a white solid.

¹H NMR (250 MHz, DMSO-*d*₆): δ_H = 7.92-7.89 (1H, m, *ArH*), 7.87-7.82 (1H, m, *ArH*), 7.40-7.27 (2H, m, *ArH*); **IR** (neat): ν (cm⁻¹) = 1547, 1387 (COO⁻).

IR spectroscopic data was found to be consistent with that reported within the literature.⁷⁵²

Sodium 4-nitrobenzoate (482)

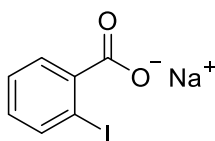


4-Nitrobenzoic acid (0.668 g, 4 mmol) was subjected to general procedure **3** to afford the title salt cleanly as a pale yellow solid.

¹H NMR (300 MHz, DMSO-*d*₆): δ_H = 8.14 (2H, d, *J* = 8.9 Hz, 2 x *CHCNO*₂), 8.05 (2H, d, *J* = 8.9 Hz, 2 x *CHCHCNO*₂); **IR** (neat): ν (cm⁻¹) = 1585 (N-O), 1522, 1404 (COO⁻), 1352 (N-O).

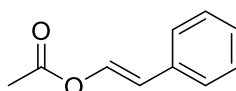
IR spectroscopic data was found to be consistent with that reported within the literature.⁷⁵⁰

Sodium 2-iodobenzoate (483)



2-Iodobenzoic acid (0.992 g, 4 mmol) was subjected to general procedure **3** to afford the title salt cleanly as a beige solid.

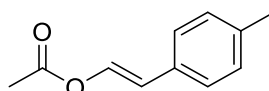
¹H NMR (300 MHz, DMSO-*d*₆): δ_H = 7.70 (1H, dd, *J* = 7.8, 1.0 Hz, *ICCH*), 7.36 (1H, dd, *J* = 7.6, 1.8 Hz, *C(O)CCH*), 7.25 (1H, app. td, *J* = 7.4, 1.1 Hz, *C(O)CCHCH*), 6.89 (1H, ddd, *J* = 7.7, 7.3, 1.8 Hz, *ICCHCH*); **IR** (neat): ν (cm⁻¹) = 1575, 1397 (COO⁻).

(E)-2-Phenylethenyl acetate (337)

(*E*)-4-Phenyl-3-buten-2-one (0.292 g, 2 mmol) was subjected to general procedure **18a** for 2 hours and the crude product was purified by flash column chromatography (eluent: Pentane:EtOAc 95:5) to afford the title compound (0.225 g, 69%) as a colourless oil.

¹H NMR (300 MHz, CDCl₃): δ_H = 7.85 (1H, d, *J* = 12.8 Hz, OCH=CH), 7.36-7.20 (5H, m, PhH), 6.39 (1H, d, *J* = 12.8 Hz, OCH=CH), 2.20 (3H, s, CH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_C = 168.1, 136.3, 134.2, 128.8, 127.5, 126.3, 115.4, 20.8; **IR** (neat): ν (cm⁻¹) = 1749 (C=O); **HRMS** (ESI-TOF): *m/z* found 163.0733, C₁₀H₁₀O₂ [M+H]⁺ requires 163.0754.

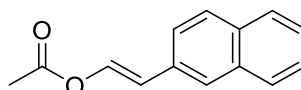
Spectroscopic data was found to be consistent with that reported within the literature.^{328,329}

(E)-2-(4-Methylphenyl)ethenyl acetate (415)

(*3E*)-4-(4-Methylphenyl)but-3-en-2-one (**391**) (0.320 g, 2 mmol) was subjected to general procedure **18a** for 2 hours and the crude product was purified by flash column chromatography (eluent: Pentane:EtOAc 96:4) to afford the title compound (0.248 g, 70%) as a colourless, crystalline solid; **mp** 52-54 °C.

¹H NMR (300 MHz, CDCl₃): δ_H = 7.81 (1H, d, *J* = 12.8 Hz, OCH=CH), 7.23 (2H, d, *J* = 8.1 Hz, 2 x CH₃CCHCH), 7.12 (2H, d, *J* = 8.0 Hz, 2 x CH₃CCH), 6.37 (1H, d, *J* = 12.8 Hz, OCH=CH), 2.33 (3H, s, ArCH₃), 2.19 (3H, s, C(O)CH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_C = 168.2, 137.4, 135.8, 131.3, 129.6, 126.3, 115.3, 21.3, 20.9; **IR** (neat): ν (cm⁻¹) = 1732 (C=O); **HRMS** (ESI-TOF): *m/z* found 199.0744, C₁₁H₁₂O₂ [M+Na]⁺ requires 199.0730.

Spectroscopic data was found to be consistent with that reported within the literature.^{328,329}

(E)-2-(Naphthalen-2-yl)ethenyl acetate (424)

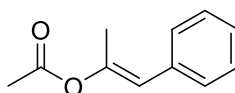
(*3E*)-4-(Naphthalen-2-yl)but-3-en-2-one (**396**) (0.393 g, 2 mmol) was subjected to general procedure **18a** for 2 hours and the crude product was purified by flash column chromatography

(eluent: Pentane:EtOAc 95:5) to afford the title compound (0.301 g, 71%) as a colourless, crystalline solid; **mp** 106-108 °C.

¹H NMR (300 MHz, CDCl₃): δ_{H} = 8.02 (1H, d, J = 12.8 Hz, OCH=CH), 7.83-7.76 (3H, m, ArH), 7.73-7.69 (1H, app. br. s, ArH), 7.54 (1H, dd, J = 8.6, 1.7 Hz, ArH), 7.52-7.42 (2H, m, ArH), 6.57 (1H, d, J = 12.8 Hz, OCH=CH), 2.23 (3H, s, CH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_{C} = 168.1, 136.6, 133.7, 132.9, 131.7, 128.5, 127.84, 127.79, 126.5, 126.1, 125.9, 123.4, 115.5, 20.9; **IR** (neat): ν (cm⁻¹) = 1750 (C=O); **HRMS** (nESI): m/z found 213.0912, C₁₄H₁₂O₂ [M+H]⁺ requires 213.0910; **GCMS** (CI, NH₃): t_{R} = 10.932 min, m/z found 230.1187, C₁₄H₁₂O₂ [M+NH₄]⁺ requires 212.0201.

Spectroscopic data was found to be consistent with that reported within the literature.³²⁸

(1E)-1-phenylprop-1-en-2-yl acetate (426)

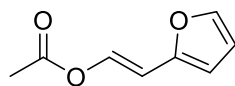


(3E)-3-Methyl-4-phenylbut-3-en-2-one (**413**) (0.320 g, 2 mmol) was subjected to general procedure **18a** for 2 hours and the crude product was purified by flash column chromatography (eluent: Pentane:EtOAc 98:2) to afford the title compound (0.231 g, 66%) as a colourless, crystalline solid; **mp** 31 °C.

¹H NMR (300 MHz, CDCl₃): δ_{H} = 7.38-7.31 (2H, m, PhH), 7.30-7.21 (3H, m, PhH), 6.27 (1H, app. s, CH₃C=CH), 2.19 (3H, s, C(O)CH₃), 2.12 (3H, d, J = 1.0 Hz, CH=CCH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_{C} = 169.6, 148.0, 134.9, 128.9, 128.4, 127.0, 118.8, 21.2, 17.2; **IR** (neat): ν (cm⁻¹) = 1750 (C=O); **HRMS** (ESI-TOF): m/z found 199.0726, C₁₁H₁₂O₂ [M+Na]⁺ requires 199.0730.

Spectroscopic data was found to be consistent with that reported within the literature.^{753,754}

(E)-2-(Furan-2-yl)ethenyl acetate (425)

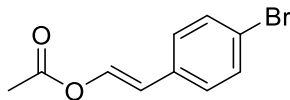


(3E)-4-(Furan-2-yl)but-3-en-2-one (**397**) (0.272 g, 2 mmol) was subjected to general procedure **18a** for 2 hours and the crude product was purified by flash column chromatography (eluent: Pentane:EtOAc 96:4) to afford the title compound (0.159 g, 52%) as a pale yellow oil.

¹H NMR (300 MHz, CDCl₃): δ_{H} = 7.83 (1H, d, J = 12.7 Hz, C(O)OCH), 7.33 (1H, d, J = 1.7 Hz, OCHCHCH), 6.36 (1H, dd, J = 3.3, 1.9 Hz, OCHCHCH), 6.22 (1H, d, J = 3.3 Hz, OCHCHCH), 6.21 (1H, d, J = 12.6 Hz, C(O)OCH=CH), 2.18 (3H, s, CH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃):

δ_{C} = 167.8, 149.5, 141.9, 135.9, 111.3, 108.1, 104.9, 20.8; **IR** (neat): ν (cm^{-1}) = 1755 (C=O); **HRMS** (ESI-TOF): m/z found 175.0371, $\text{C}_8\text{H}_8\text{O}_3$ $[\text{M}+\text{Na}]^+$ requires 175.0366.

(E)-2-(4-Bromophenyl)ethenyl acetate (416)

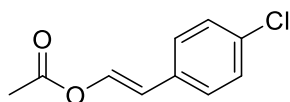


(3E)-4-(4-Bromophenyl)but-3-en-2-one (**392**) (0.450 g, 2 mmol) was subjected to general procedure **18a** for 2 hours and the crude product was purified by flash column chromatography (eluent: Pentane:EtOAc 95:5) to afford the title compound (0.335 g, 69%) as a colourless, crystalline solid; **mp** 70-71 °C.

^1H NMR (250 MHz, CDCl_3): δ_{H} = 7.84 (1H, d, J = 12.8 Hz, $\text{OCH}=\text{CH}$), 7.42 (2H, d, J = 8.5 Hz, 2 x BrCCH), 7.18 (2H, d, J = 8.4 Hz, 2 x BrCCHCH), 6.31 (1H, d, J = 12.8 Hz, $\text{OCH}=\text{CH}$), 2.19 (3H, s, CH_3); **$^{13}\text{C}\{^1\text{H}\}$ NMR** (75.5 MHz, CDCl_3): δ_{C} = 168.0, 136.7, 133.2, 131.9, 127.8, 121.2, 114.3, 20.8; **IR** (neat): ν (cm^{-1}) = 1753 (C=O); **HRMS** (ESI-TOF): m/z found 240.9875, $\text{C}_{10}\text{H}_9\text{O}_2\text{Br}$ $[\text{M}+\text{H}]^+$ requires 240.9859.

Spectroscopic data was found to be consistent with that reported within the literature.³²⁸

(E)-2-(4-Chlorophenyl)ethenyl acetate (417)

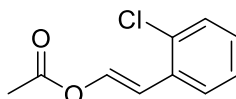


(3E)-4-(4-Chlorophenyl)but-3-en-2-one (**393**) (0.361 g, 2 mmol) was subjected to general procedure **18a** for 2 hours and the crude product was purified by flash column chromatography (eluent: Pentane:EtOAc 96:4) to afford the title compound (0.278 g, 71%) as a colourless, crystalline solid; **mp** 66-68 °C.

^1H NMR (300 MHz, CDCl_3): δ_{H} = 7.84 (1H, d, J = 12.8 Hz, $\text{OCH}=\text{CH}$), 7.31-7.22 (4H, m, ArH), 6.34 (1H, d, J = 12.8 Hz, $\text{OCH}=\text{CH}$), 2.20 (3H, s, CH_3); **$^{13}\text{C}\{^1\text{H}\}$ NMR** (75.5 MHz, CDCl_3): δ_{C} = 168.0, 136.7, 133.1, 132.7, 128.9, 127.5, 114.2, 20.8; **IR** (neat): ν (cm^{-1}) = 1754 (C=O); **HRMS** (ESI-TOF): m/z found 197.0401, $\text{C}_{10}\text{H}_9\text{O}_2\text{Cl}$ $[\text{M}+\text{H}]^+$ requires 197.0364.

Spectroscopic data was found to be consistent with that reported within the literature.^{328,329}

(E)-2-(2-Chlorophenyl)ethenyl acetate (427)

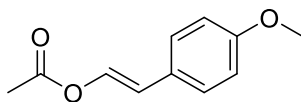


(3*E*)-4-(2-Chlorophenyl)but-3-en-2-one (**394**) (0.361 g, 2 mmol) was subjected to general procedure **18a** for 2 hours and the crude product was purified by flash column chromatography (eluent: Pentane:EtOAc 96:4) to afford the title compound (0.213 g, 54%) as a pale yellow oil.

¹H NMR (300 MHz, CDCl₃): δ_H = 7.82 (1H, d, *J* = 12.8 Hz, OCH=CH), 7.50-7.43 (1H, m, Ar*H*), 7.39-7.32 (1H, m, Ar*H*), 7.25-7.13 (2H, m, Ar*H*), 6.76 (1H, d, *J* = 12.8 Hz, OCH=CH), 2.21 (3H, s, CH₃); ¹³C{¹H} NMR (75.5 MHz, CDCl₃): δ_C = 168.0, 137.8, 133.2, 132.5, 129.9, 128.7, 127.1, 126.7, 112.1, 20.8; IR (neat): ν (cm⁻¹) = 1756 (C=O); HRMS (ESI-TOF): *m/z* found 197.0369, C₁₀H₉O₂Cl [M+H]⁺ requires 197.0364.

Spectroscopic data was found to be consistent with that reported within the literature.³²⁹

(*E*)-2-(4-Methoxyphenyl)ethenyl acetate (414)

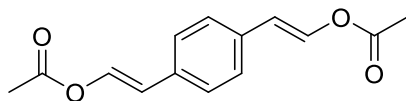


(3*E*)-4-(4-Methoxyphenyl)but-3-en-2-one (**390**) (0.352 g, 2 mmol) was subjected to general procedure **18a** for 2 hours and the crude product was purified by flash column chromatography (eluent: Pentane:EtOAc 96:4) to afford the title compound (0.239 g, 62%) as an off-white solid; mp 51-54 °C (lit. 52-54 °C).³²⁹

¹H NMR (300 MHz, CDCl₃): δ_H = 7.75 (1H, d, *J* = 12.8 Hz, OCH=CH), 7.27 (2H, d, *J* = 8.7 Hz, 2 x OCCHCH), 6.86 (2H, d, *J* = 8.7 Hz, 2 x OCCH), 6.36 (1H, d, *J* = 12.8 Hz, OCH=CH), 3.80 (3H, s, OCH₃), 2.18 (3H, s, C(O)CH₃); ¹³C{¹H} NMR (75.5 MHz, CDCl₃): δ_C = 168.2, 159.2, 134.9, 127.5, 126.6, 114.9, 114.3, 55.3, 20.8; IR (neat): ν (cm⁻¹) = 1734 (C=O); HRMS (ESI-TOF): *m/z* found 193.0858, C₁₁H₁₂O₃ [M+H]⁺ requires 193.0859.

Spectroscopic data was found to be consistent with that reported within the literature.³²⁹

(*E*)-2-{4-[(*E*)-2-(Acetyloxy)ethenyl]phenyl}ethenyl acetate (430)

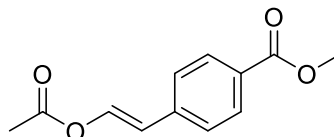


(3*E*)-4-{4-[(1*E*)-3-Oxobut-1-en-1-yl]phenyl}but-3-en-2-one (**402**) (0.429 g, 2 mmol) was subjected to a modified version of general procedure **18a** for 2 hours, in which double the amount of *m*CPBA (1.344 g, 6.0 mmol, 3.0 equiv.) and double the amount of toluene (14 mL) was used. The crude product was purified by flash column chromatography (eluent: Pentane:EtOAc 96:4) to afford the title compound (0.146 g, 30%) as a white solid; mp 118-120 °C.

¹H NMR (250 MHz, CDCl₃): δ_H = 7.85 (2H, d, *J* = 12.8 Hz, 2 x OCH=CH), 7.27 (4H, s, ArH), 6.36 (2H, d, *J* = 12.8 Hz, 2 x OCH=CH), 2.19 (6H, s, 2 x CH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_C = 168.1, 136.3, 133.4, 126.6, 115.0, 20.9; **IR** (neat): ν (cm⁻¹) = 1736 (C=O); **HRMS** (ESI-TOF): *m/z* found 269.0779, C₁₄H₁₄O₄ [M+Na]⁺ requires 269.0784.

Spectroscopic data was found to be consistent with that reported within the literature.³²⁸

Methyl 4-[(*E*)-2-(acetyloxy)ethenyl]benzoate (418)

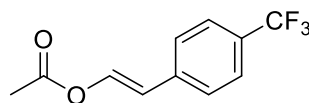


Methyl 4-[(1*E*)-3-oxobut-1-en-1-yl]benzoate (**398**) (0.408 g, 2 mmol) was subjected to general procedure **18a** for 24 hours and the crude product was purified by flash column chromatography (eluent: Pentane:EtOAc 92:8) to afford the title compound (0.241 g, 55%) as a white solid; **mp** 72-73 °C.

¹H NMR (300 MHz, CDCl₃): δ_H = 7.95 (2H, d, *J* = 8.4 Hz, 2 x C(O)CCH), 7.93 (1H, d, *J* = 12.8 Hz, OCH=CH), 7.36 (2H, d, *J* = 8.3 Hz, 2 x C(O)CCHCH), 6.38 (1H, d, *J* = 12.8 Hz, OCH=CH), 3.89 (3H, s, OCH₃), 2.19 (3H, s, C(O)CH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_C = 167.9, 166.8, 139.0, 138.0, 130.1, 128.9, 126.1, 114.4, 52.2, 20.8; **IR** (neat): ν (cm⁻¹) = 1757 (C=O vinyl ester), 1707 (C=O methyl ester); **HRMS** (ESI-TOF): *m/z* found 243.0642, C₁₂H₁₂O₄ [M+Na]⁺ requires 243.0628.

Spectroscopic data was found to be consistent with that reported within the literature.³²⁸

(*E*)-2-[4-(Trifluoromethyl)phenyl]ethenyl acetate (419)

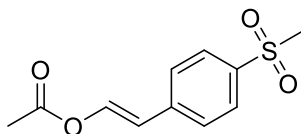


(3*E*)-4-[4-(Trifluoromethyl)phenyl]but-3-en-2-one (**399**) (0.428 g, 2 mmol) was subjected to general procedure **18a** for 24 hours and the crude product was purified by flash column chromatography (eluent: Pentane:EtOAc 96:4) to afford the title compound (0.245 g, 53%) as a colourless, crystalline solid; **mp** 45-47 °C.

¹H NMR (300 MHz, CDCl₃): δ_H = 7.93 (1H, d, *J* = 12.8 Hz, OCH=CH), 7.55 (2H, d, *J* = 8.3 Hz, 2 x CF₃CCH), 7.41 (2H, d, *J* = 8.3 Hz, 2 x CF₃CCHCH), 6.40 (1H, d, *J* = 12.8 Hz, OCH=CH), 2.21 (3H, s, CH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_C = 167.9, 138.0 (app. d, ⁴*J*_{CF} = 1.4 Hz), 137.9, 129.3 (q, ²*J*_{CF} = 32.5 Hz), 126.4, 125.8 (q, ³*J*_{CF} = 3.8 Hz), 124.2 (q, ¹*J*_{CF} = 271.8 Hz), 114.1, 20.8; **IR** (neat): ν (cm⁻¹) = 1690 (C=O).

Spectroscopic data was found to be consistent with that reported within the literature.³²⁸

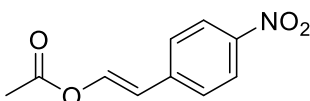
(*E*)-2-(4-Methanesulfonylphenyl)ethenyl acetate (420)



(3*E*)-4-(4-Methanesulfonylphenyl)but-3-en-2-one (**395**) (0.224 g, 1 mmol) was subjected to general procedure **18b** for 24 hours but on half the scale detailed within the method and the crude product was purified by flash column chromatography (eluent: Pentane:EtOAc 65:35) to afford the title compound (0.083 g, 35%) as a white solid; **mp** 86-88 °C.

¹H NMR (300 MHz, CDCl₃): δ_H = 7.97 (1H, d, *J* = 12.8 Hz, OCH=CH), 7.86 (2H, d, *J* = 8.5 Hz, 2 x S(O)₂CCH), 7.49 (2H, d, *J* = 8.4 Hz, 2 x S(O)₂CCHCH), 6.41 (1H, d, *J* = 12.8 Hz, OCH=CH), 3.04 (3H, s, S(O)₂CH₃), 2.21 (3H, s, C(O)CH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_C = 167.8, 140.2, 138.94, 138.91, 128.0, 126.9, 113.6, 44.7, 20.8; **IR** (neat): ν (cm⁻¹) = 1748 (C=O); **HRMS** (ESI-TOF): *m/z* found 263.0338, C₁₁H₁₂O₄S [M+Na]⁺ requires 263.0349.

(*E*)-2-(4-Nitrophenyl)ethenyl acetate (421)



(3*E*)-4-(4-Nitrophenyl)but-3-en-2-one (**400**) (0.382 g, 2 mmol) was subjected to general procedure **18b** for 24 hours and the crude product was purified by flash column chromatography (eluent: Pentane:EtOAc 92:8) to afford the title compound (0.187 g, 45%) as a white solid; **mp** 124-126 °C (lit. 98-100 °C).⁷⁵⁵

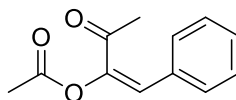
¹H NMR (300 MHz, CDCl₃): δ_H = 8.14 (2H, d, *J* = 8.8 Hz, 2 x CHCNO₂), 7.98 (1H, d, *J* = 12.8 Hz, OCH=CH), 7.44 (2H, d, *J* = 8.8 Hz, 2 x CHCHCNO₂), 6.41 (1H, d, *J* = 12.8 Hz, OCH=CH), 2.21 (3H, s, CH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_C = 167.7, 146.8, 141.4, 139.3, 126.7, 124.2, 113.4, 20.7; **IR** (neat): ν (cm⁻¹) = 1757 (C=O), 1502 (N-O), 1337 (N-O); **HRMS** (nESI): *m/z* found 225.0872, C₁₀H₉NO₄ [M+NH₄]⁺ requires 225.0870; **GCMS** (CI, NH₃): *t*_R = 10.276 min, *m/z* found 225.0866, C₁₀H₉NO₄ [M+NH₄]⁺ requires 225.0875.

In some instances, the *Z*-stereoisomer was observed in small quantities (< 3%), as identified from the following discernible peaks observed within the NMR spectra:

¹H NMR (300 MHz, CDCl₃): δ_H = 7.70 (1H, d, *J* = 8.9 Hz, Ar*H*), 5.75 (1H, d, *J* = 7.3, OCH=CH), 2.31 (3H, s, CH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_C = 137.0, 129.7, 123.8.

Spectroscopic data was found to be consistent with that reported within the literature.³²⁸

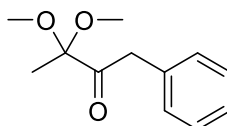
(1E)-3-Oxo-1-phenylbut-1-en-2-yl acetate (433)



3-Benzylidene-2,4-pentanedione (0.348 mL, 2 mmol) was subjected to general procedure **18b** for 24 hours and the crude product was purified by flash column chromatography (eluent: Pentane:EtOAc 98:2) to afford the title compound (0.225 g, 55%) as a colourless oil.

¹H NMR (300 MHz, CDCl₃): δ_{H} = 7.39-7.27 (5H, m, PhH), 6.89 (1H, s, OC=CH), 2.23 (3H, s, CC(O)CH₃), 2.04 (3H, s, OC(O)CH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_{C} = 195.8, 169.6, 145.5, 132.6, 129.2, 129.1, 128.7, 126.7, 29.0, 20.4; **IR** (neat): ν (cm⁻¹) = 1756 (C=O ester), 1693 (C=O ketone); **HRMS** (ESI-TOF): m/z found 227.0662, C₁₂H₁₂O₃ [M+Na]⁺ requires 227.0679.

3,3-Dimethoxy-1-phenylbutan-2-one (434)

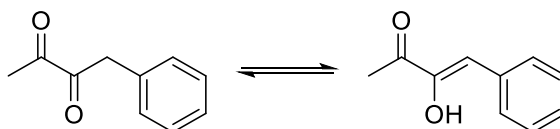


The following was based on a literature procedure published by Narasaka *et al.*⁴⁵⁵ To a stirring mixture of K₂CO₃ (0.691 g, 5 mmol) in MeOH (4.2 mL) was added a solution of (1E)-3-Oxo-1-phenylbut-1-en-2-yl acetate (**433**) (0.102 g, 0.5 mmol) in MeOH (1.4 mL) at room temperature. The resulting mixture was then stirred for 10 minutes before being quenched with H₂O. After separating the two layers, the aqueous phase was extracted three times with Et₂O. The combined organic phases were then dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (eluent: Pentane:EtOAc 95:5) to afford the title compound (0.060 g, 58%) as a pale yellow oil.

¹H NMR (300 MHz, CDCl₃): δ_{H} = 7.36-7.18 (5H, m, PhH), 3.91 (2H, s, CH₂), 3.25 (6H, s, 2 x OCH₃), 1.36 (3H, s, CCH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_{C} = 206.5, 134.0, 129.9, 128.6, 127.0, 103.0, 49.9, 44.7, 20.2; **IR** (neat): ν (cm⁻¹) = 1735 (C=O); **HRMS** (ESI-TOF): m/z found 231.1054, C₁₂H₁₆O₃ [M+Na]⁺ requires 231.0992.

Spectroscopic data was found to be consistent with that reported within the literature.⁴⁵⁵

1-Phenylbutane-2,3-dione (435a) and (3Z)-3-Hydroxy-4-phenylbut-3-en-2-one (435b)



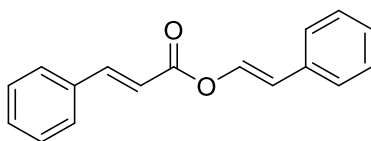
The following was based on a literature procedure published by Montevecchi *et al.*⁴⁵⁶ A stirring solution of (1*E*)-3-Oxo-1-phenylbut-1-en-2-yl acetate (**433**) (0.057 g, 0.28 mmol) in 5 M HCl:1,4-dioxane (1:2, 5 mL total) was heated under reflux (95 °C) for 30 minutes. After cooling to room temperature, the reaction was quenched with 10% aqueous K₂CO₃ solution and extracted with Et₂O. The combined organic phases were dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (eluent: Pentane:EtOAc 95:5→50:50) to afford the title compound (0.027 g, 59%) as a yellow oil.

Ketone **435a** and enol **435b** tautomeric forms were observed within the ¹H NMR spectrum in a 13:87 ratio.

¹H NMR (250 MHz, CDCl₃): δ_H = 7.88-7.80 (2H, m, major, PhH), 7.45-7.19 (3H, m, major, PhH; 5H, m, minor, PhH), 6.46 (1H, d, *J* = 1.0 Hz, major, C(O)CCH), 4.05 (2H, s, minor, CH₂), 2.51 (3H, s, major, CH₃), 2.32 (3H, s, minor, CH₃).

Spectroscopic data was found to be consistent with that reported within the literature.^{455,457,458}

(*E*)-2-Phenylethenyl (2*E*)-3-phenylprop-2-enoate (444**)**

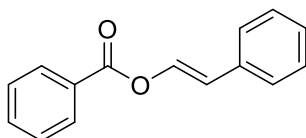


(*E,E*)-Dibenzylideneacetone (0.469 g, 2 mmol) was subjected to general procedure **18a** for 24 hours and the crude product was purified by flash column chromatography (eluent: Pentane:EtOAc 97:3) to afford the title compound (0.106 g, 21%) as an off-white solid; **mp** 94-97 °C.

¹H NMR (300 MHz, CDCl₃): δ_H = 8.03 (1H, d, *J* = 12.8 Hz, OCH=CH), 7.85 (1H, d, *J* = 16.0 Hz, C(O)CH=CH), 7.62-7.54 (2H, m, PhH), 7.46-7.30 (7H, m, PhH), 7.28-7.21 (1H, m, PhH), 6.52 (1H, d, *J* = 16.0 Hz, C(O)CH), 6.51 (1H, d, *J* = 12.8 Hz, OCH=CH); ¹³C{¹H} NMR (75.5 MHz, CDCl₃): δ_C = 164.1, 146.9, 136.5, 134.4, 134.2, 131.0, 129.1, 128.9, 128.5, 127.5, 126.4, 116.6, 115.6; **IR** (neat): ν (cm⁻¹) = 1717 (C=O); **HRMS** (ESI-TOF): *m/z* found 273.0886, C₁₇H₁₄O₂ [M+Na]⁺ requires 273.0886.

Spectroscopic data was found to be consistent with that reported within the literature.⁷⁵⁶

(*E*)-2-Phenylethenyl benzoate (316**)**

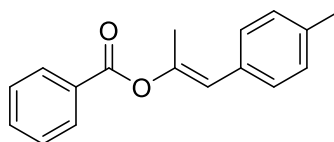


(*E*)-Chalcone (0.417 g, 2 mmol) was subjected to general procedure **18a** for 24 hours and the crude product was purified by flash column chromatography (eluent: Pentane:EtOAc 97:3) to afford the title compound (0.192 g, 43%) as a white solid; **mp** 58-59 °C (lit. 62 °C).³⁶⁹

¹H NMR (300 MHz, CDCl₃): δ_H = 8.17-8.12 (2H, m, PhH), 8.10 (1H, d, *J* = 12.8, OCH=CH), 7.64-7.57 (1H, m, PhH), 7.52-7.44 (2H, m, PhH), 7.42-7.29 (4H, m, PhH), 7.28-7.21 (1H, m, PhH), 6.59 (1H, d, *J* = 12.8 Hz, OCH=CH); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_C = 163.7, 136.6, 134.2, 133.8, 130.1, 129.0, 128.9, 128.7, 127.6, 126.4, 115.9; **IR** (neat): ν (cm⁻¹) = 1724 (C=O); **HRMS** (ESI-TOF): *m/z* found 247.0736, C₁₅H₁₂O₂ [M+Na]⁺ requires 247.0730.

Spectroscopic data was found to be consistent with that reported within the literature.^{329,757}

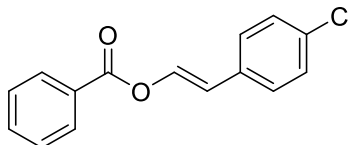
(1*E*)-1-(4-Methylphenyl)prop-1-en-2-yl benzoate (449)



2-Methyl-3-(*p*-tolyl)acrylophenone (0.095 g, 0.4 mmol) was subjected to general procedure **18a** for 24 hours but on a fifth of the scale detailed within the method and the crude product was purified by flash column chromatography (eluent: Pentane:EtOAc 98:2) to afford the title compound (0.045 g, 45%) as a colourless oil.

¹H NMR (300 MHz, CDCl₃): δ_H = 8.17-8.11 (2H, m, ArH), 7.65-7.58 (1H, m, ArH), 7.53-7.46 (2H, m, ArH), 7.26-7.15 (4H, m, ArH), 6.37 (1H, app. s, OCCH), 2.37 (3H, s, ArCH₃), 2.24 (3H, d, *J* = 0.9 Hz, OCCH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_C = 165.3, 147.7, 136.8, 133.5, 132.1, 130.1, 130.0, 129.2, 128.8, 128.6, 119.0, 21.3, 17.4; **IR** (neat): ν (cm⁻¹) = 1729 (C=O); **HRMS** (ESI-TOF): *m/z* found 275.1048, C₁₇H₁₆O₂ [M+Na]⁺ requires 275.1043.

(*E*)-2-(4-Chlorophenyl)ethenyl benzoate (450)

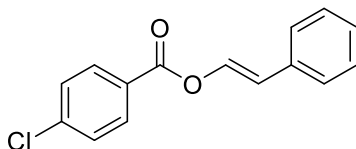


4-Chlorochalcone (0.485 g, 2 mmol) was subjected to general procedure **18a** for 24 hours and the crude product was purified by flash column chromatography (eluent: Pentane:EtOAc 97:3) to afford the title compound (0.211 g, 41%) as a white solid; **mp** 125-126 °C.

¹H NMR (500 MHz, CDCl₃): δ_H = 8.16-8.13 (2H, m, ArH), 8.08 (1H, d, *J* = 12.8 Hz, OCH=CH), 7.65-7.60 (1H, m, ArH), 7.52-7.47 (2H, m, ArH), 7.33-7.28 (4H, m, ArH), 6.53 (1H, d, *J* = 12.8 Hz, OCH=CH); **¹³C{¹H} NMR** (125.8 MHz, CDCl₃): δ_C = 163.6, 136.9, 133.8, 133.2, 132.8,

130.1, 129.0, 128.8, 128.7, 127.5, 114.8; **IR** (neat): ν (cm^{-1}) = 1717 (C=O); **HRMS** (nESI): m/z found 276.0789, $\text{C}_{15}\text{H}_{11}\text{O}_2\text{Cl}$ $[\text{M}+\text{NH}_4]^+$ requires 276.0786; **GCMS** (CI, NH_3): t_R = 12.579 min, m/z found 276.0791, $\text{C}_{15}\text{H}_{11}\text{O}_2\text{Cl}$ $[\text{M}+\text{NH}_4]^+$ requires 276.0791.

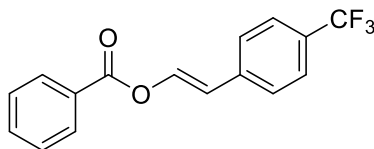
(E)-2-Phenylethenyl 4-chlorobenzoate (451)



4'-Chlorochalcone (0.485 g, 2 mmol) was subjected to general procedure **18a** for 24 hours and the crude product was purified by flash column chromatography (eluent: Pentane:EtOAc 97:3) to afford the title compound (0.227 g, 44%) as a white, crystalline solid; **mp** 85-87 °C.

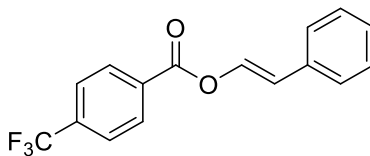
^1H NMR (500 MHz, CDCl_3): δ_H = 8.08 (2H, d, J = 8.7 Hz, 2 x ClCCHCH), 8.07 (1H, d, J = 12.8 Hz, OCH=CH), 7.47 (2H, d, J = 8.7 Hz, 2 x ClCCH), 7.41-7.37 (2H, m, PhH), 7.36-7.32 (2H, m, PhH), 7.29-7.24 (1H, m, PhH), 6.59 (1H, d, J = 12.8 Hz, OCH=CH); **$^{13}\text{C}\{^1\text{H}\}$ NMR** (125.8 MHz, CDCl_3): δ_C = 162.9, 140.3, 136.4, 134.1, 131.5, 129.1, 128.9, 127.7, 127.5, 126.4, 116.3; **IR** (neat): ν (cm^{-1}) = 1721 (C=O); **GCMS** (CI, NH_3): t_R = 12.343 min, m/z found 276.0791, $\text{C}_{15}\text{H}_{11}\text{O}_2\text{Cl}$ $[\text{M}+\text{NH}_4]^+$ requires 276.0791.

(E)-2-[4-(Trifluoromethyl)phenyl]ethenyl benzoate (452)



(*E*)-1-Phenyl-3-[4-(trifluoromethyl)phenyl]prop-2-en-1-one (**406**) (0.553 g, 2 mmol) was subjected to general procedure **18a** for 24 hours and the crude product was purified by flash column chromatography (eluent: Pentane:EtOAc 97:3) to afford the title compound (0.153 g, 26%) as a white, crystalline solid; **mp** 112-114 °C.

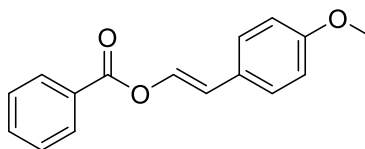
^1H NMR (500 MHz, CDCl_3): δ_H = 8.18 (1H, d, J = 12.9 Hz, OCH=CH), 8.17-8.14 (2H, m, ArH), 7.66-7.62 (1H, m, ArH), 7.59 (2H, d, J = 8.3 Hz, ArH), 7.53-7.47 (4H, m, ArH), 6.61 (1H, d, J = 12.8 Hz, OCH=CH); **$^{13}\text{C}\{^1\text{H}\}$ NMR** (125.8 MHz, CDCl_3): δ_C = 163.6, 138.3, 138.1 (app. d, $^4J_{\text{CF}}$ = 1.4 Hz), 134.0, 130.2, 129.4 (q, $^2J_{\text{CF}}$ = 32.5 Hz), 128.8, 128.7, 126.5, 125.8 (q, $^3J_{\text{CF}}$ = 3.8 Hz), 124.3 (q, $^1J_{\text{CF}}$ = 271.9 Hz), 114.7; **IR** (neat): ν (cm^{-1}) = 1729 (C=O); **HRMS** (nESI): m/z found 293.0787, $\text{C}_{16}\text{H}_{11}\text{O}_2\text{F}_3$ $[\text{M}+\text{H}]^+$ requires 293.0784; **GCMS** (CI, NH_3): t_R = 11.140 min, m/z found 310.1061, $\text{C}_{16}\text{H}_{11}\text{O}_2\text{F}_3$ $[\text{M}+\text{NH}_4]^+$ requires 310.1055.

(E)-2-Phenylethenyl 4-(trifluoromethyl)benzoate (453)

(2E)-3-Phenyl-1-[4-(trifluoromethyl)phenyl]prop-2-en-1-one (**407**) (0.553 g, 2 mmol) was subjected to general procedure **18a** for 24 hours and the crude product was purified by flash column chromatography (eluent: Pentane:EtOAc 97:3) to afford the title compound (0.316 g, 54%) as a white, crystalline solid; **mp** 113-115 °C.

¹H NMR (500 MHz, CDCl₃): δ_H = 8.26 (2H, d, *J* = 8.2 Hz, 2 x CF₃CCH), 8.10 (1H, d, *J* = 12.7 Hz, OCH=CH), 7.76 (2H, d, *J* = 8.2 Hz, 2 x CF₃CCHCH), 7.43-7.39 (2H, m, PhH), 7.38-7.34 (2H, m, PhH), 7.31-7.27 (1H, m, PhH), 6.64 (1H, d, *J* = 12.8 Hz, OCH=CH); **¹³C{¹H} NMR** (125.8 MHz, CDCl₃): δ_C = 162.5, 136.3, 135.1 (q, ²*J*_{CF} = 32.7 Hz), 133.9, 132.3, 130.5, 128.9, 127.9, 126.5, 125.7 (q, ³*J*_{CF} = 3.6 Hz), 123.7 (q, ¹*J*_{CF} = 272.8 Hz), 116.7; **IR** (neat): ν (cm⁻¹) = 1723 (C=O); **GCMS** (CI, NH₃): *t*_R = 10.864 min, *m/z* found 310.1055, C₁₆H₁₁O₂F₃ [M+NH₄]⁺ requires 310.1055.

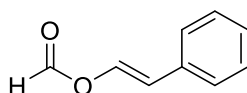
Spectroscopic data was found to be consistent with that reported within the literature.⁷⁵⁸

(E)-2-(4-Methoxyphenyl)ethenyl benzoate (454)

4-Methoxychalcone (0.477 g, 2 mmol) was subjected to general procedure **18a** for 24 hours and the crude product was purified by flash column chromatography (eluent: Pentane:EtOAc 97:3) to afford the title compound (0.077 g, 15%) as a white, crystalline solid; **mp** 81-83 °C.

¹H NMR (300 MHz, CDCl₃): δ_H = 8.18-8.12 (2H, m, PhH), 8.01 (1H, d, *J* = 12.7 Hz, OCH=CH), 7.66-7.58 (1H, m, PhH), 7.53-7.46 (2H, m, PhH), 7.34 (2H, d, *J* = 8.7 Hz, 2 x OCCHCH), 6.89 (2H, d, *J* = 8.8 Hz, 2 x OCCH), 6.56 (1H, d, *J* = 12.7 Hz, OCH=CH), 3.82 (3H, s, CH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_C = 163.9, 159.2, 135.2, 133.7, 130.1, 129.1, 128.7, 127.6, 126.7, 115.6, 114.3, 55.4; **IR** (neat): ν (cm⁻¹) = 1724 (C=O); **HRMS** (ESI-TOF): *m/z* found 277.0816, C₁₆H₁₄O₃ [M+Na]⁺ requires 277.0835.

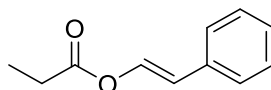
Spectroscopic data was found to be consistent with that reported within the literature.⁷⁵⁸

(E)-2-Phenylethenyl formate (455)

(*E*)-Cinnamaldehyde (0.252 mL, 2 mmol) was subjected to general procedure **18a** for 2 hours and the crude product was purified by flash column chromatography (eluent: Pentane:EtOAc 96:4) to afford the title compound (0.179 g, 61%) as a colourless oil.

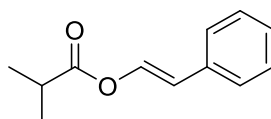
¹H NMR (300 MHz, CDCl₃): δ_H = 8.12 (1H, s, C(O)H), 7.93 (1H, d, *J* = 12.7 Hz, OCH=CH), 7.38-7.24 (5H, m, PhH), 6.52 (1H, d, *J* = 12.8 Hz, OCH=CH); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_C = 157.8, 134.7, 133.6, 128.9, 127.9, 126.5, 117.1; **IR** (neat): ν (cm⁻¹) = 1727 (C=O); **HRMS** (nESI): *m/z* found 149.0594, C₉H₈O₂ [M+H]⁺ requires 149.0597.

Spectroscopic data was found to be consistent with that reported within the literature.^{328,413}

(E)-2-Phenylethenyl propanoate (456)

(1*E*)-1-Phenylpent-1-en-3-one (**403**) (0.320 g, 2 mmol) was subjected to general procedure **18a** for 2 hours and the crude product was purified by flash column chromatography (eluent: Pentane:EtOAc 96:4) to afford the title compound (0.256 g, 73%) as a colourless crystalline solid; **mp** 33-35 °C.

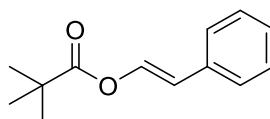
¹H NMR (300 MHz, CDCl₃): δ_H = 7.88 (1H, d, *J* = 12.8, OCH=CH), 7.35-7.18 (5H, m, PhH), 6.39 (1H, d, *J* = 12.8, OCH=CH), 2.46 (2H, q, *J* = 7.5 Hz, CH₂), 1.21 (3H, t, *J* = 7.5 Hz, CH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_C = 171.6, 136.4, 134.3, 128.8, 127.4, 126.3, 115.1, 27.4, 8.9; **IR** (neat): ν (cm⁻¹) = 1749 (C=O); **HRMS** (ESI-TOF): *m/z* found 199.0730, C₁₁H₁₂O₂ [M+Na]⁺ requires 199.0730.

(E)-2-Phenylethenyl 2-methylpropanoate (457)

(1*E*)-4-Methyl-1-phenylpent-1-en-3-one (**404**) (0.348 g, 2 mmol) was subjected to general procedure **18a** for 2 hours and the crude product was purified by flash column chromatography (eluent: Pentane:EtOAc 97:3) to afford the title compound (0.252 g, 66%) as a tacky, white solid.

¹H NMR (300 MHz, CDCl₃): δ_H = 7.87 (1H, d, *J* = 12.8 Hz, OCH=CH), 7.35-7.18 (5H, m, PhH), 6.40 (1H, d, *J* = 12.8 Hz, OCH=CH), 2.67 (1H, sept., *J* = 7.0 Hz, CH₃CH), 1.24 (6H, d, *J* = 7.0 Hz, 2 x CH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_C = 174.2, 136.5, 134.3, 128.8, 127.4, 126.3, 115.2, 34.0, 18.8; **IR** (neat): ν (cm⁻¹) = 1747 (C=O); **HRMS** (ESI-TOF): *m/z* found 213.0836, C₁₂H₁₄O₂ [M+Na]⁺ requires 213.0886.

(*E*)-2-Phenylethenyl 2,2-dimethylpropanoate (458)

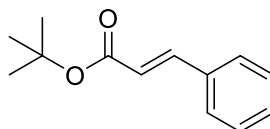


(1*E*)-4,4-Dimethyl-1-phenylpent-1-en-3-one (**405**) (0.377 g, 2 mmol) was subjected to general procedure **18a** for 2 hours and the crude product was purified by flash column chromatography (eluent: Pentane:Et₂O 98:2) to afford the title compound (0.105 g, 26%) as a colourless oil.

¹H NMR (300 MHz, CDCl₃): δ_H = 7.85 (1H, d, *J* = 12.8 Hz, OCH=CH), 7.37-7.19 (5H, m, PhH), 6.42 (1H, d, *J* = 12.8, OCH=CH), 1.30 (9H, s, 3 x CH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_C = 175.7, 136.8, 134.4, 128.8, 127.4, 126.3, 115.2, 38.9, 27.1; **IR** (neat): ν (cm⁻¹) = 1742 (C=O); **HRMS** (ESI-TOF): *m/z* found 227.1055, C₁₃H₁₆O₂ [M+Na]⁺ requires 227.1043.

Spectroscopic data was found to be consistent with that reported within the literature.⁷⁵⁹

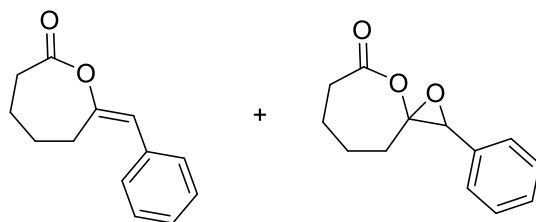
tert-Butyl (2*E*)-3-phenylprop-2-enoate (463)



The title compound was formed as a regioisomeric by-product in the synthesis of (*E*)-2-phenylethenyl 2,2-dimethylpropanoate (**458**) from (1*E*)-4,4-dimethyl-1-phenylpent-1-en-3-one (**405**) and was isolated in small quantities by flash column chromatography.

¹H NMR (250 MHz, CDCl₃): δ_H = 7.59 (1H, d, *J* = 16.0 Hz, C(O)CH=CH), 7.54-7.46 (2H, m, PhH), 7.42-7.33 (3H, m, PhH), 6.37 (1H, d, *J* = 16.0 Hz, C(O)CH), 1.53 (9H, s, 3 x CH₃).

Spectroscopic data was found to be consistent with that reported within the literature.⁴⁶¹

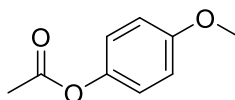
(7E)-7-(Phenylmethylidene)oxepan-2-one (465) and 2-Phenyl-1,4-dioxaspiro[2.6]nonan-5-one (466)

2-Benzylidenecyclohexan-1-one (0.373 g, 2 mmol) was subjected to general procedure **18a** for 10 minutes and the crude product was purified by flash column chromatography (eluent: Pentane:EtOAc 90:10) to afford an inseparable mixture of the title compounds as a white crystalline solid. Attempt 1: The title compounds (0.384 g) were formed in a 96:4 ratio in favour of lactone **465**; Attempt 2: The title compounds (0.320 g) were formed in an 84:16 ratio in favour of lactone **465**.

Lactone 465: ^1H NMR (300 MHz, CDCl_3): δ_{H} = 7.44-7.23 (5H, m, PhH), 6.45 (1H, s, OC=CH), 2.74-2.65 (2H, m, CCH₂), 2.64-2.55 (2H, m, CCH₂), 2.00-1.81 (4H, m, 2 x CCH₂CH₂); $^{13}\text{C}\{^1\text{H}\}$ NMR (75.5 MHz, CDCl_3): δ_{C} = 173.3, 151.7, 134.4, 128.7, 128.5, 127.5, 119.3, 33.9, 29.8, 27.9, 23.3; **IR** (neat): ν (cm^{-1}) = 1745 (br., C=O); **HRMS** (ESI-TOF): m/z 225.0890, C₁₃H₁₄O₂ [M+Na]⁺ requires 225.0886.

Epoxy lactone 466: ^1H NMR (300 MHz, CDCl_3): δ_{H} = 7.44-7.23 (5H, m, PhH), 4.37 (1H, s, OCH), 2.96-2.84 (1H, m, C(O)CH_AH_B), 2.83-2.72 (1H, m, C(O)CH_AH_B), 2.08-1.63 (6H, m, 3 x CH₂); $^{13}\text{C}\{^1\text{H}\}$ NMR (75.5 MHz, CDCl_3): δ_{C} = 173.5, 133.0, 128.6, 126.2, 86.9, 64.8, 35.6, 27.4, 24.0, 23.0 (one aromatic signal not discernible); **IR** (neat): ν (cm^{-1}) = 1745 (br., C=O); **HRMS** (ESI-TOF): m/z found 241.0829, C₁₃H₁₄O₃ [M+Na]⁺ requires 241.0835.

Spectroscopic data was found to be consistent with that reported within the literature.⁷⁶⁰

4-Methoxyphenyl acetate (469)

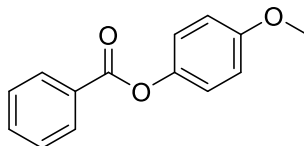
4'-Methoxyacetophenone (0.300 g, 2 mmol) was subjected to general procedure **18a** for 2 hours and the crude product was purified by flash column chromatography (eluent: Pentane:EtOAc 92:8) to afford the title compound (0.290 g, 87%) as a colourless, crystalline solid; **mp** 33-35 °C (lit. 33-34 °C).⁷⁶¹

^1H NMR (300 MHz, CDCl_3): δ_{H} = 7.01 (2H, d, J = 9.1 Hz, 2 x C(O)OCCH), 6.89 (2H, d, J = 9.1 Hz, 2 x CH₃OCCH), 3.79 (3H, s, OCH₃), 2.27 (3H, s, C(O)CH₃); $^{13}\text{C}\{^1\text{H}\}$ NMR (75.5 MHz,

CDCl_3): $\delta_{\text{C}} = 170.0, 157.3, 144.2, 122.4, 114.5, 55.6, 21.1$; **IR** (neat): ν (cm^{-1}) = 1742 (C=O); **HRMS** (ESI-TOF): m/z found 189.0503, $\text{C}_9\text{H}_{10}\text{O}_3$ $[\text{M}+\text{Na}]^+$ requires 189.0528.

Spectroscopic data was found to be consistent with that reported within the literature.⁷⁶²

4-Methoxyphenyl benzoate (377)

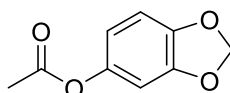


4-Methoxybenzophenone (0.424 g, 2 mmol) was subjected to general procedure **18a** for 6 hours and the crude product was purified by flash column chromatography (eluent: Pentane:EtOAc 94:6) to afford the title compound (0.306 g, 67%) as a white, crystalline solid; **mp** 89-90 °C (lit. 89-90 °C).⁷⁶³

^1H NMR (250 MHz, CDCl_3): $\delta_{\text{H}} = 8.25\text{--}8.19$ (2H, m, PhH), 7.68-7.60 (1H, m, PhH), 7.56-7.47 (2H, m, PhH), 7.15 (2H, d, $J = 9.1$ Hz, 2 x C(O)OCCH), 6.96 (2H, d, $J = 9.1$ Hz, 2 x CH_3OCCH), 3.83 (3H, s, CH_3); **$^{13}\text{C}\{^1\text{H}\}$ NMR** (75.5 MHz, CDCl_3): $\delta_{\text{C}} = 165.7, 157.4, 144.5, 133.6, 130.3, 129.8, 128.7, 122.6, 114.6, 55.7$; **IR** (neat): ν (cm^{-1}) = 1730 (C=O); **HRMS** (ESI-TOF): m/z found 229.0860, $\text{C}_{14}\text{H}_{12}\text{O}_3$ $[\text{M}+\text{H}]^+$ requires 229.0859.

Spectroscopic data was found to be consistent with that reported within the literature.⁷⁶⁴

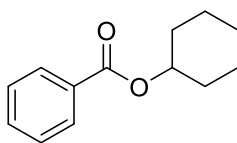
2H-1,3-Benzodioxol-5-yl acetate (470)



3',4'-(Methylenedioxy)acetophenone (0.328 g, 2 mmol) was subjected to general procedure **18a** for 6 hours and the crude product was purified by flash column chromatography (eluent: Pentane:EtOAc 92:8) to afford the title compound (0.293 g, 81%) as a colourless oil.

^1H NMR (300 MHz, CDCl_3): $\delta_{\text{H}} = 6.76$ (1H, d, $J = 8.4$ Hz, C(O)OCCHCH), 6.60 (1H, d, $J = 2.3$ Hz, C(O)OCCHC), 6.52 (1H, dd, $J = 8.4, 2.3$ Hz, C(O)OCCHCH), 5.96 (2H, s, CH_2), 2.26 (3H, s, CH_3); **$^{13}\text{C}\{^1\text{H}\}$ NMR** (75.5 MHz, CDCl_3): $\delta_{\text{C}} = 169.9, 148.0, 145.4, 145.0, 114.0, 108.0, 103.8, 101.8, 21.0$; **IR** (neat): ν (cm^{-1}) = 1757 (C=O); **HRMS** (ESI-TOF): m/z found 203.0327, $\text{C}_9\text{H}_8\text{O}_4$ $[\text{M}+\text{Na}]^+$ requires 203.0315.

Spectroscopic data was found to be consistent with that reported within the literature.⁷⁶⁵

Cyclohexyl benzoate (254)

To a vigorously stirring suspension of *m*CPBA (0.672 g, 3 mmol, 1.5 equiv.) in toluene (7 mL) was added DMAP (0.049 g, 0.4 mmol, 20 mol%) and cyclohexyl phenyl ketone (0.377 g, 2 mmol). The resulting mixture was stirred at room temperature for 6 hours. After this period, the standard work-up procedure was then applied. Based on a literature procedure,⁴⁶⁵ to a stirring solution of the crude residue in MeOH (2 mL) was added NaBH₄ (0.057 g, 1.5 mmol) at room temperature. The resulting mixture was then stirred for 2 hours before being poured into a separating funnel containing H₂O (2 mL) and EtOAc (4 mL). The resulting layers were separated and the aqueous phase was then extracted three times with EtOAc. The combined organic phases were washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (eluent: Pentane:EtOAc 97:3) to afford the title compound in 96% purity (0.215 g, 53%) as a pale yellow oil.

Regioisomers **254** and **255** were observed within the ¹H NMR spectrum in a 96:4 ratio, as determined by comparison of the integrals for the triplet of triplets at 5.03 and 2.56 ppm respectively.

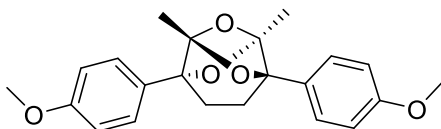
¹H NMR (300 MHz, CDCl₃): δ_H = 8.08-8.03 (2H, m, PhH), 7.58-7.51 (1H, m, PhH), 7.47-7.39 (2H, m, PhH), 5.03 (1H, tt, *J* = 8.8, 3.8 Hz, OCH), 2.01-1.88 (2H, m, CyH), 1.86-1.73 (2H, m, CyH), 1.71-1.52 (3H, m, CyH), 1.52-1.23 (3H, m, CyH); ¹³C{¹H} NMR (75.5 MHz, CDCl₃): δ_C = 166.1, 132.8, 131.1, 129.7, 128.4, 73.2, 31.8, 25.6, 23.8; IR (neat): ν (cm⁻¹) = 1713 (C=O); HRMS (ESI-TOF): *m/z* found 227.1045, C₁₃H₁₆O₂ [M+Na]⁺ requires 227.1043.

Phenyl cyclohexanecarboxylate (255) minor impurity (4%):

¹H NMR (300 MHz, CDCl₃): δ_H = 2.56 (1H, tt, *J* = 11.2, 3.7 Hz, C(O)CH)

Spectroscopic data was found to be consistent with that reported within the literature.⁴⁶²⁻⁴⁶⁴

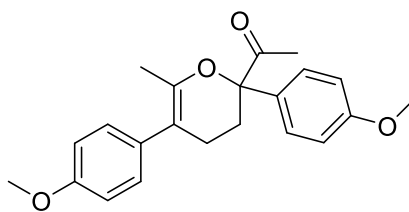
(1*S*,3*R*,6*R*,8*S*)-3,6-Bis(4-methoxyphenyl)-1,8-dimethyl-2,7,9-trioxatricyclo[4.3.0.0^{3,8}]nonane (487)



To a vigorously stirring suspension of *m*CPBA (0.672 g, 3 mmol, 3.0 equiv.) in toluene (7 mL) was added 1-[2,5-bis(4-methoxyphenyl)-6-methyl-3,4-dihydro-2*H*-pyran-2-yl]ethan-1-one (**492**) (0.352 g, 1 mmol). The resulting mixture was stirred at room temperature for 2 hours. The standard work-up procedure was then applied and the crude product was purified by flash column chromatography (eluent: Pentane:EtOAc 93:7) to afford the title compound (0.074 g, 20%) as a white solid; **mp** 194-195 °C. Recrystallisation of **487** from toluene at room temperature afforded colourless crystals suitable for single crystal X-ray diffraction analysis.

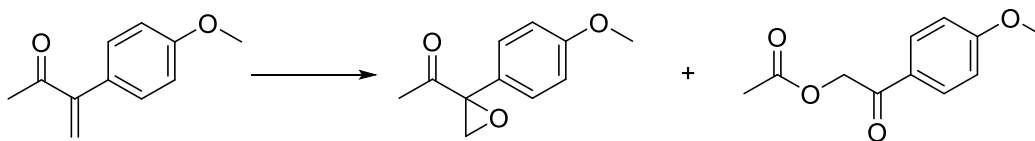
¹H NMR (300 MHz, CDCl₃): δ_H = 7.32 (4H, d, *J* = 8.9 Hz, 4 x OCCHCH), 6.90 (4H, d, *J* = 8.9 Hz, 4 x OCCH), 3.81 (6H, s, 2 x OCH₃), 2.58-2.46 (2H, m, 2 x CH_AH_B), 2.23-2.11 (2H, m, 2 x CH_AH_B), 1.25 (6H, s, 2 x CCH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_C = 159.3, 132.3, 127.1, 113.7, 112.9, 84.5, 55.4, 26.8, 15.5; **IR** (neat): ν (cm⁻¹) = 2968, 2939, 2839 (C-H), 1514 (C=C aromatic); **HRMS** (ESI-TOF): *m/z* found 391.1514, C₂₂H₂₄O₅ [M+Na]⁺ requires 391.1516.

1-[2,5-Bis(4-methoxyphenyl)-6-methyl-3,4-dihydro-2*H*-pyran-2-yl]ethan-1-one (492)

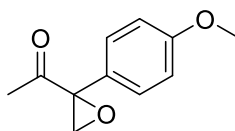


Upon standing neat at room temperature (*ca.* 1 month), 3-(4-methoxyphenyl)but-3-en-2-one (**485**) was found to undergo self-dimerisation *via* a [4+2] cycloaddition reaction to form 1-[2,5-bis(4-methoxyphenyl)-6-methyl-3,4-dihydro-2*H*-pyran-2-yl]ethan-1-one (**492**). Purification by flash column chromatography (eluent: Pentane:EtOAc 93:7) afforded the title compound as a pale yellow solid; **mp** 89-90 °C.

¹H NMR (300 MHz, CDCl₃): δ_H = 7.44 (2H, d, *J* = 9.0 Hz, Ar*H*), 7.04 (2H, d, *J* = 8.8 Hz, Ar*H*), 6.91 (2H, d, *J* = 8.9 Hz, Ar*H*), 6.84 (2H, d, *J* = 8.8 Hz, Ar*H*), 3.81 (3H, s, OCH₃), 3.79 (3H, s, OCH₃), 2.66-2.56 (1H, m, OCCH_AH_B), 2.36-2.20 (1H, m, OCCH_AH_B), 2.17 (3H, s, C(O)CH₃), 2.15-2.03 (2H, m, OCCH₂CH₂), 1.96 (3H, s, C=CCH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_C = 209.5, 159.4, 158.1, 145.7, 133.8, 131.4, 129.8, 126.5, 114.0, 113.6, 110.9, 85.5, 55.34, 55.31, 30.0, 25.1, 24.4, 18.2; **IR** (neat): ν (cm⁻¹) = 3056, 3030, 3002, 2951, 2911, 2833 (C-H), 1712 (C=O), 1508 (C=C aromatic); **HRMS** (ESI-TOF): *m/z* found 375.1569, C₂₂H₂₄O₄ [M+Na]⁺ requires 375.1567.

Experimental procedure for the oxidation of 3-(4-methoxyphenyl)but-3-en-2-one 485

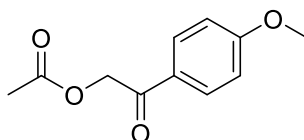
To a vigorously stirring suspension of *m*CPBA (0.336 g, 1.5 mmol, 1.5 equiv.) in toluene (3.5 mL) was added 3-(4-methoxyphenyl)but-3-en-2-one (**485**) (0.176 g, 1 mmol). The resulting mixture was stirred at room temperature for 24 hours. The standard work-up procedure was then applied and the crude residue, which contained a separable mixture of 1-[2-(4-methoxyphenyl)oxiran-2-yl]ethan-1-one (**488**) and 2-(4-methoxyphenyl)-2-oxoethyl acetate (**493**), was then purified by flash column chromatography (eluent: Pentane:EtOAc 80:20).

1-[2-(4-Methoxyphenyl)oxiran-2-yl]ethan-1-one (488)

Following the procedure above, the title compound was isolated as a pale yellow oil.

¹H NMR (300 MHz, CDCl₃): δ_H = 7.38 (2H, d, *J* = 8.9 Hz, 2 x OCCHCH), 6.90 (2H, d, *J* = 8.9 Hz, 2 x OCCH), 3.81 (3H, s, OCH₃), 3.26 (1H, d, *J* = 5.5 Hz, CH_AH_B), 3.05 (1H, d, *J* = 5.5 Hz, CH_AH_B), 2.19 (3H, s, C(O)CH₃); **¹³C{¹H} NMR** (125.8 MHz, CDCl₃): δ_C = 205.5, 159.9, 128.8, 126.4, 114.0, 63.2, 55.4, 53.4, 25.3; **IR** (neat): ν (cm⁻¹) = 1712 (C=O), 1515 (C=C aromatic); **HRMS** (ESI-TOF): *m/z* found 215.0677, C₁₁H₁₂O₃ [M+Na]⁺ requires 215.0679.

Spectroscopic data was found to be consistent with that reported within the literature.⁴⁷⁸

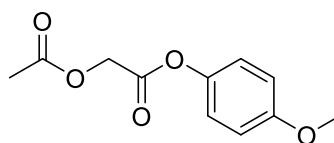
2-(4-Methoxyphenyl)-2-oxoethyl acetate (493)

Following the procedure above, the title compound was isolated as a colourless solid; **mp** 56-58 °C (lit. 58-59 °C).⁷⁶⁶

¹H NMR (300 MHz, CDCl₃): δ_H = 7.90 (2H, d, *J* = 9.0 Hz, 2 x OCCHCH), 6.96 (2H, d, *J* = 9.0 Hz, 2 x OCCH), 5.30 (2H, s, OCH₂), 3.88 (3H, s, OCH₃), 2.23 (3H, s, C(O)CH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_C = 190.7, 170.7, 164.2, 130.2, 127.3, 114.2, 65.9, 55.7, 20.8; **IR** (neat): ν (cm⁻¹) = 1746 (C=O ester), 1691 (C=O ketone); **HRMS** (ESI-TOF): *m/z* found 231.0621, C₁₁H₁₂O₄ [M+Na]⁺ requires 231.0633.

Spectroscopic data was found to be consistent with that reported within the literature.⁴⁸⁵

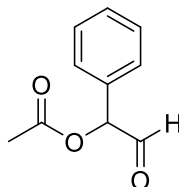
4-Methoxyphenyl 2-(acetyloxy)acetate (**497**)



To a vigorously stirring suspension of *m*CPBA (1.153 g, 5.15 mmol, 3.0 equiv.) in toluene (8.5 mL) was added 3-(4-methoxyphenyl)but-3-en-2-one (**485**) (0.302 g, 1.72 mmol). The resulting mixture was stirred at room temperature for 48 hours. The standard work-up procedure was then applied and the crude product was purified by flash column chromatography (eluent: Pentane:EtOAc 90:10) to afford the title compound (0.182 g, 47%) as a colourless oil.

¹H NMR (300 MHz, CDCl₃): δ_H = 7.03 (2H, d, *J* = 9.1 Hz, 2 x C(O)OCCH), 6.88 (2H, d, *J* = 9.1 Hz, 2 x CH₃OCCH), 4.82 (2H, s, OCH₂), 3.80 (3H, s, OCH₃), 2.19 (3H, s, C(O)CH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_C = 170.5, 166.9, 157.7, 143.7, 122.2, 114.7, 60.9, 55.7, 20.6; **IR** (neat): ν (cm⁻¹) = 1776 (C=O aromatic ester), 1749 (C=O aliphatic ester); **HRMS** (ESI-TOF): *m/z* found 247.0567, C₁₁H₁₂O₅ [M+Na]⁺ requires 247.0582.

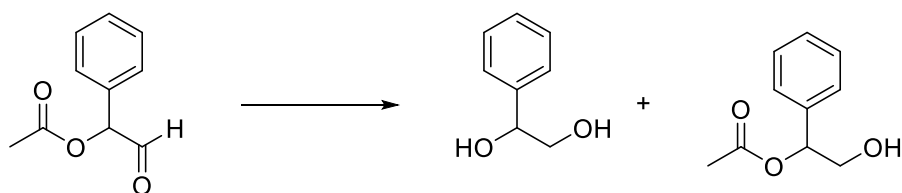
2-Oxo-1-phenylethyl acetate (**341**)



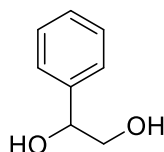
To a vigorously stirring suspension of *m*CPBA (2.958 g, 13.2 mmol, 1.2 equiv.) in toluene (38.5 mL) was added (*E*)-2-phenylethenyl acetate (**337**) (1.784 g, 11 mmol). The resulting mixture was stirred at room temperature for 24 hours. The standard work-up procedure was then applied and the crude product was purified by flash column chromatography (eluent: Pentane:EtOAc 90:10 → 50:50) to afford the title compound (0.779 g, 40%) as a colourless oil.

¹H NMR (250 MHz, CDCl₃): δ_H = 9.56 (1H, s, C(O)H), 7.48-7.35 (5H, m, PhH), 6.05 (1H, s, PhCH), 2.24 (3H, s, CH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_C = 194.1, 170.2, 131.2, 129.6, 129.4, 128.2, 80.6, 20.8; **IR** (neat): ν (cm⁻¹) = 1736 (C=O ester), 1702 (C=O aldehyde); **HRMS** (ESI-TOF): *m/z* found 201.0511, C₁₀H₁₀O₃ [M+Na]⁺ requires 201.0522.

Spectroscopic data was found to be consistent with that reported within the literature.⁴⁰⁷

Experimental procedure for the reduction of 2-oxo-1-phenylethyl acetate **341**

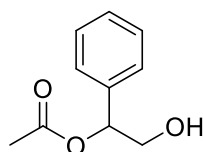
The following was based on a literature procedure published by Toru *et al.*⁴⁰⁸ To a stirring solution of 2-oxo-1-phenylethyl acetate (**341**) (0.178 g, 1 mmol) in THF (4 mL) was added LiAlH₄ solution (5.0 mL, 1 M in THF, 5.0 equiv., 5 mmol) dropwise at 0 °C. The resulting mixture was allowed to warm gradually to room temperature and was stirred for a further 3 hours. The reaction was then quenched with aqueous 1 M HCl and was extracted three times with Et₂O. The combined organic phases were then dried over MgSO₄, filtered and concentrated *in vacuo*. The crude residue, which contained a separable mixture of 1-phenylethane-1,2-diol (**342**) and 2-hydroxy-1-phenylethyl acetate (**343**), was then purified by flash column chromatography (eluent: Pentane:EtOAc 25:75).

1-Phenylethane-1,2-diol (342**)**

Following the procedure above, the title compound (0.079 g, 57%) was isolated as a white, crystalline solid; **mp** 61-62 °C (lit. 61 °C).⁷⁶⁷

¹H NMR (300 MHz, CDCl₃): δ_H = 7.39-7.27 (5H, m, PhH), 4.83 (1H, dd, *J* = 8.1, 3.6 Hz, PhCH), 3.77 (1H, dd, *J* = 11.2, 3.0 Hz, CH_AH_B), 3.67 (1H, dd, *J* = 11.3, 8.2 Hz, CH_AH_B), 2.28-2.18 (2H, br. s, 2 x OH); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_C = 140.6, 128.7, 128.2, 126.2, 74.8, 68.2; **IR** (neat): ν (cm⁻¹) = 3324 (O-H); **HRMS** (ESI-TOF): *m/z* found 161.0563, C₈H₁₀O₂ [M+Na]⁺ requires 161.0573.

Spectroscopic data was found to be consistent with that reported within the literature.⁷⁶⁸

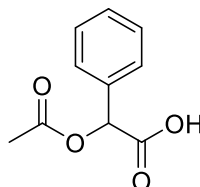
2-Hydroxy-1-phenylethyl acetate (343**)**

Following the procedure above, the title compound was isolated as a colourless oil.

¹H NMR (300 MHz, CDCl₃): δ_{H} = 7.42-7.28 (5H, m, PhH), 4.96 (1H, dd, J = 8.4, 3.3, PhCH), 4.28 (1H, dd, J = 11.6, 3.3, CH_AH_B), 4.15 (1H, dd, J = 11.6, 8.5, CH_AH_B), 2.11 (3H, s, CH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_{C} = 171.4, 139.8, 128.7, 128.4, 126.3, 72.5, 69.5, 21.1; **IR** (neat): ν (cm⁻¹) = 3447 (O-H), 1736 (C=O); **HRMS** (ESI-TOF): m/z found 203.0672, C₁₀H₁₂O₃ [M+Na]⁺ requires 203.0679.

Spectroscopic data was found to be consistent with that reported within the literature.⁷⁶⁹

2-(Acetyloxy)-2-phenylacetic acid (353)

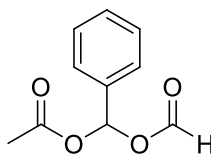


To a vigorously stirring suspension of *m*CPBA (0.560 g, 2.5 mmol, 2.5 equiv.) in toluene (5 mL) was added (*E*)-4-phenyl-3-buten-2-one (0.146 g, 1 mmol). The resulting mixture was stirred at room temperature for 2 hours. The standard work-up procedure was then applied and the crude residue was purified by flash column chromatography (eluent: Pentane:EtOAc 70:30), with the title compound isolated as a white solid.

¹H NMR (300 MHz, CDCl₃): δ_{H} = 7.52-7.45 (2H, m, PhH), 7.43-7.36 (3H, m, PhH), 7.10-6.40 (1H, br. s, OH), 5.94 (1H, s, PhCH), 2.19 (3H, s, CH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_{C} = 174.0, 170.5, 133.3, 129.6, 129.0, 127.8, 74.2, 20.8; **IR** (neat): ν (cm⁻¹) = 3036 (O-H), 1724 (br., C=O); **HRMS** (ESI-TOF): m/z found 217.0475, C₁₀H₁₀O₄ [M+Na]⁺ requires 217.0477.

Spectroscopic data was found to be consistent with that reported within the literature.⁴¹²

(Formyloxy)(phenyl)methyl acetate (354)



Synthesis from (*E*)-4-phenyl-3-buten-2-one (336)

To a vigorously stirring suspension of *m*CPBA (3.586 g, 16 mmol, 4.0 equiv.) in toluene (44 mL) was added (*E*)-4-phenyl-3-buten-2-one (0.585 g, 4 mmol). The resulting mixture was stirred at room temperature for 48 hours. The standard work-up procedure was then applied and the crude product was purified by flash column chromatography (eluent: Pentane:EtOAc 95:5) to afford the title compound (0.566 g, 73%) as a colourless oil.

Large scale synthesis from (*E*)-4-phenyl-3-buten-2-one (336)

This procedure was repeated on a 40 mmol scale with respect to (*E*)-4-phenyl-3-buten-2-one to afford the title compound (3.911 g, 50%) as a colourless oil

Alternative large scale procedure from (*E*)-4-phenyl-3-buten-2-one (336)

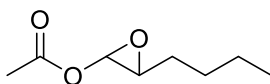
To a vigorously stirring suspension of *m*CPBA (35.859 g, 160 mmol, 4.0 equiv.) in toluene (200 mL) was added (*E*)-4-phenyl-3-buten-2-one (5.848 g, 40 mmol). The resulting mixture was stirred at room temperature for 24 hours. The precipitate was then removed by filtration and the filtrate was washed 4 times with saturated aqueous Na₂CO₃ solution. The aqueous washings were then extracted with EtOAc and the combined organic phases were dried over MgSO₄, filtered and concentrated *in vacuo* to afford the title compound (6.500 g, 84%) as a colourless oil.

Synthesis from 2-oxo-1-phenylethyl acetate (341)

To a vigorously stirring suspension of *m*CPBA (0.336 g, 1.5 mmol, 1.5 equiv.) in toluene (3.5 mL) was added 2-oxo-1-phenylethyl acetate (**341**) (0.178 g, 1 mmol). The resulting mixture was stirred at room temperature for 24 hours. The standard work-up procedure was then applied and the crude product was purified by flash column chromatography (eluent: Pentane:EtOAc 95:5) to afford the title compound (0.103 g, 53%) as a colourless oil.

¹H NMR (300 MHz, CDCl₃): δ_H = 8.11 (1H, d, *J* = 0.9 Hz, C(O)*H*), 7.76 (1H, app. s, Ph*CH*), 7.57-7.50 (2H, m, Ph*H*), 7.46-7.40 (3H, m, Ph*H*), 2.15 (3H, s, CH₃); ¹³C{¹H} NMR (75.5 MHz, CDCl₃): δ_C = 168.9, 158.9, 134.8, 130.2, 128.8, 126.8, 89.4, 21.0; IR (neat): ν (cm⁻¹) = 1750 (C=O), 1733 (C=O); HRMS (ESI-TOF): *m/z* found 217.0479, C₁₀H₁₀O₄ [M+Na]⁺ requires 217.0471.

Spectroscopic data was found to be consistent with that reported within the literature.⁴¹³

3-Butyloxiran-2-yl acetate (498)

To a vigorously stirring suspension of *m*CPBA (3.589 g, 16 mmol, 4.0 equiv.) in toluene (44 mL) was added (*E*)-3-octen-2-one (0.589 mL, 4 mmol). The resulting mixture was stirred at room temperature for 48 hours. The standard work-up procedure was then applied and the crude product was purified by flash column chromatography (eluent: Pentane:EtOAc 97:3) to afford the title compound (0.416 g, 66%) as a colourless oil.

¹H NMR (300 MHz, CDCl₃): δ_H = 5.32 (1H, d, *J* = 0.8 Hz, CHCHCH₂), 3.09 (1H, td, *J* = 5.7, 0.8 Hz, CHCHCH₂), 2.09 (3H, s, C(O)CH₃), 1.61-1.49 (2H, m, CHCH₂), 1.49-1.28 (4H, m,

$\text{CH}_2\text{CH}_2\text{CH}_3$), 0.90 (3H, t, $J = 7.1$ Hz, CH_2CH_3); $^{13}\text{C}\{^1\text{H}\}$ NMR (75.5 MHz, CDCl_3): $\delta_{\text{C}} = 170.8$, 76.7, 57.6, 29.4, 27.4, 22.4, 21.0, 14.0; IR (neat): ν (cm^{-1}) = 2959, 2934, 2865 (C-H), 1757 (C=O), 1213, 1042 (C-O); HRMS (nESI): m/z found 159.1013, $\text{C}_8\text{H}_{14}\text{O}_3$ $[\text{M}+\text{H}]^+$ requires 159.1016.

5.3 Experimental procedures and compound characterisation data for Chapter 3

5.3.1 Procedures for optimisation of formylation methodology

General Procedure 21: *Optimisation for the formylation of benzylamine (Section 3.3.1)*

To a stirring mixture of (formyloxy)(phenyl)methyl acetate **354** (1.0 or 1.5 equiv. as detailed) and any specified solvent was added benzylamine in a single portion. The resulting mixture was then stirred at room temperature for the specified period of time before being concentrated *in vacuo*, with the rotary evaporator water bath set at room temperature. Conversions were determined by analysis of the ^1H NMR spectra obtained in CDCl_3 for the crude reaction mixture. The ratio of species present was determined by comparison of the integrals for the peaks at 3.87, 4.42 + 4.49 (minor + major rotamers) and 4.89 ppm attributable to benzylamine, *N*-benzylformamide **525** and *N*-benzylidenebenzylamine **526** respectively.

General procedure 22: *Optimisation for the formylation of 2-phenylethanol (Table 37)*

(Formyloxy)(phenyl)methyl acetate **354** (0.291 g, 1.5 mmol, 1.5 equiv.) was added to a Radleys carousel tube and if specified this was dissolved in EtOAc (1 mL). NaHCO_3 (0.168 g, 2 mmol, 2.0 equiv.) was then added if required. To the stirring mixture, 2-phenylethanol (0.120 mL, 1 mmol) was added, the tube was sealed and the reaction was stirred at either room temperature or 40 °C, as specified, for 24 hours. Where necessary, the reaction mixture was then allowed to cool to room temperature and reactions run in the presence of NaHCO_3 were dissolved in CH_2Cl_2 and filtered. Any solvent was then removed *in vacuo*. Conversions were determined by analysis of the ^1H NMR spectra obtained in CDCl_3 for the crude reaction mixture. Specifically, this was achieved by comparing the integrals of the peaks at 3.89 and 4.41 ppm attributable to 2-phenylethanol and 2-phenylethyl formate **563** respectively.

Experimental procedure for the formylation of L-valine (Scheme 286)

To a stirring solution of L-valine (0.117 g, 1 mmol) and NaHCO_3 (0.336 g, 4 mmol, 4.0 equiv.) in D_2O (5 mL) was added (formyloxy)(phenyl)methyl acetate **354** (0.291 g, 1.5 mmol, 1.5 equiv.) in a single portion. The resulting mixture was stirred at room temperature for 24 hours. An aliquot of the crude reaction mixture was then removed for ^1H NMR spectroscopic analysis to determine the conversion into *N*-formyl-L-valine **560**. Specifically, this was determined by comparison of the integrals for the peaks at 3.61 and 3.79 + 4.14 (minor + major rotamers) ppm attributable to L-valine and *N*-formyl-L-valine **560** respectively.

Experimental procedure for kinetic profiling by ^1H NMR spectroscopy (Figure 65)

To an NMR tube containing a d_8 -toluene solution (1.2 mL) of (formyloxy)(phenyl)methyl acetate **354** (0.182 g, 0.938 mmol, 1.5 equiv.) was added benzylamine (0.068 mL, 0.625 mmol). The reaction progress as a function of time, specifically the formation and consumption of *N*-benzylidenebenzylamine **526**, was then monitored by ^1H NMR spectroscopy; with acquisitions being performed at 5 minute intervals over a 120 minute time period commencing at 15 minutes.

5.3.2 General procedures for formamide synthesis

General Procedure 23a: *Formylations requiring no solvent*

(Formyloxy)(phenyl)methyl acetate **354** (0.583 g, 3 mmol, 1.5 equiv.) and the appropriate amine (2 mmol) were combined and stirred neat for 1 hour at room temperature. The reaction mixture was then dissolved in the minimum amount of the column eluent and loaded directly onto a silica gel flash column for purification to afford the desired formamide.

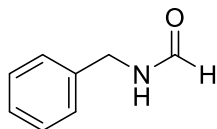
General Procedure 23b: *Formylations run in ethyl acetate*

To a stirring solution of (formyloxy)(phenyl)methyl acetate **354** (0.583 g, 3 mmol, 1.5 equiv.) in EtOAc (2 mL) was added the appropriate amine (2 mmol) in a single portion. The reaction mixture was then stirred for the specified period of time at room temperature. With the exception of compounds eluted with 100% EtOAc, the reaction mixture was then concentrated *in vacuo*, with the rotary evaporator water bath set at room temperature, and the residue was dissolved in the minimum amount of the column eluent. In all cases, the solution was then loaded onto a silica gel flash column for purification to afford the desired formamide.

5.3.3 Experimental Data

(m) and (M) are used to denote minor and major formamide rotamers respectively within the ^{13}C NMR assignment. In some instances the minor rotamer may not be fully assigned due to low intensity or overlapping peaks.

N-Benzylformamide (525)



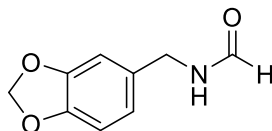
Benzylamine (0.218 mL, 2 mmol) was subjected to general procedure **23a** and purification by flash column chromatography (eluent: CH_2Cl_2 :EtOAc 70:30) afforded the title compound (0.241 g, 89%) as an off-white solid; **mp** 60-61 °C (lit. 59-61 °C).⁷⁷⁰

Two rotamers were observed within the NMR spectra in an 86:14 ratio.

^1H NMR (300 MHz, CDCl_3): δ_{H} = 8.22 (1H, s, major, $\text{C}(\text{O})\text{H}$), 8.13 (1H, d, J = 11.9 Hz, minor, $\text{C}(\text{O})\text{H}$), 7.44-7.24 (5H, m, major + minor, PhH), 6.63-6.31 (1H, br. s, major, NH), 6.31-6.11 (1H, br. s, minor, NH), 4.47 (2H, d, J = 6.0 Hz, major, CH_2), 4.40 (2H, d, J = 6.5 Hz, minor, CH_2); **$^{13}\text{C}\{^1\text{H}\}$ NMR** (75.5 MHz, CDCl_3): δ_{C} = 164.9 (m), 161.3 (M), 137.7 (M), 137.5 (m), 128.9 (m), 128.8 (M), 128.0 (m), 127.8 (M), 127.6 (M), 127.0 (m), 45.7 (m), 42.1 (M); **IR** (neat): ν (cm^{-1}) = 3268 (N-H), 1636 (C=O); **HRMS** (ESI-TOF): m/z found 158.0588, $\text{C}_8\text{H}_9\text{NO}$ $[\text{M}+\text{Na}]^+$ requires 158.0582.

Spectroscopic data was found to be consistent with that reported within the literature.^{581,614}

N-(2*H*-1,3-Benzodioxol-5-ylmethyl)formamide (538)



Piperonylamine (0.249 mL, 2 mmol) was subjected to general procedure **23a** and purification by flash column chromatography (eluent: CH_2Cl_2 :EtOAc 70:30) afforded the title compound (0.294 g, 82%) as an off-white, crystalline solid; **mp** 96-98 °C (lit. 96-97 °C).⁷⁷¹

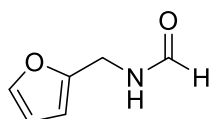
Two rotamers were observed within the NMR spectra in an 86:14 ratio.

^1H NMR (300 MHz, CDCl_3): δ_{H} = 8.20 (1H, s, major, $\text{C}(\text{O})\text{H}$), 8.12 (1H, d, J = 11.9 Hz, minor, $\text{C}(\text{O})\text{H}$), 6.79-6.66 (3H, m, major + minor, ArH), 6.20-5.98 (1H, br. s, major + minor, NH), 5.95 (2H, s, minor, OCH_2), 5.93 (2H, s, major, OCH_2), 4.35 (2H, d, J = 5.9 Hz, major, NCH_2), 4.29

(2H, d, $J = 6.5$ Hz, minor, NCH_2); $^{13}\text{C}\{^1\text{H}\}$ NMR (75.5 MHz, CDCl_3): $\delta_{\text{C}} = 164.6$ (m), 161.1 (M), 148.2 (m), 148.0 (M), 147.4 (m), 147.1 (M), 131.5 (M), 131.4 (m), 121.2 (M), 120.4 (m), 108.5 (m), 108.44 (M), 108.41 (M), 107.6 (m), 101.3 (m), 101.2 (M), 45.6 (m), 42.0 (M); IR (neat): ν (cm^{-1}) = 3262 (N-H), 1648 (C=O); HRMS (ESI-TOF): m/z found 180.0662, $\text{C}_9\text{H}_9\text{NO}_3$ $[\text{M}+\text{H}]^+$ requires 180.0661.

Spectroscopic data was found to be consistent with that reported within the literature.⁷⁷²

***N*-(Furan-2-ylmethyl)formamide (539)**



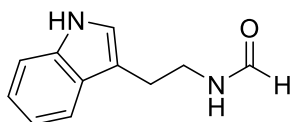
Furfurylamine (0.177 mL, 2 mmol) was subjected to general procedure **23a** and purification by flash column chromatography (eluent: CH_2Cl_2 :EtOAc 75:25) afforded the title compound (0.203 g, 81%) as a yellow oil.

Two rotamers were observed within the NMR spectra in an 87:13 ratio.

^1H NMR (300 MHz, CDCl_3): $\delta_{\text{H}} = 8.22$ (1H, s, major, $\text{C}(\text{O})\text{H}$), 8.18 (1H, d, $J = 11.9$ Hz, minor, $\text{C}(\text{O})\text{H}$), 7.38 (1H, dd, $J = 1.8, 0.8$ Hz, minor, ArH), 7.36 (1H, dd, $J = 1.8, 0.8$ Hz, major, ArH), 6.35-6.31 (1H, m, major + minor, ArH), 6.27-6.22 (1H, m, major + minor, ArH), 6.11-5.73 (1H, br. s, major + minor, NH), 4.48 (2H, d, $J = 5.7$ Hz, major, CH_2), 4.37 (2H, d, $J = 6.4$ Hz, minor, CH_2); $^{13}\text{C}\{^1\text{H}\}$ NMR (75.5 MHz, CDCl_3): $\delta_{\text{C}} = 165.2$ (m), 161.3 (M), 150.7 (M), 142.9 (m), 142.3 (M), 110.6 (m), 110.5 (M), 107.7 (M), 107.6 (m), 39.0 (m), 35.1 (M); IR (neat): ν (cm^{-1}) = 3284 (N-H), 1653 (C=O); HRMS (ESI-TOF): m/z found 126.0556, $\text{C}_6\text{H}_7\text{NO}_2$ $[\text{M}+\text{H}]^+$ requires 126.0555.

Spectroscopic data was found to be consistent with that reported within the literature.^{773,774}

***N*-[2-(1*H*-Indol-3-yl)ethyl]formamide (540)**



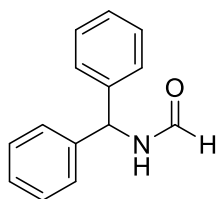
Tryptamine (0.320 g, 2 mmol) was subjected to general procedure **23b** for 1 hour and purification by flash column chromatography (eluent: EtOAc) afforded the title compound (0.340 g, 90%) as a pale brown, highly viscous oil.

Two rotamers were observed within the NMR spectra in an 82:18 ratio.

¹H NMR (300 MHz, CDCl₃): δ_{H} = 8.45-8.29 (1H, br. s, major + minor, CHNH), 8.07 (1H, d, J = 1.2 Hz, major, C(O)H), 7.86 (1H, d, J = 12.1 Hz, minor, C(O)H), 7.60 (1H, d, J = 7.9 Hz, major, ArH), 7.55 (1H, d, J = 8.2 Hz, minor, ArH), 7.39-7.35 (1H, m, major + minor, ArH), 7.25-7.18 (1H, m, major + minor, ArH), 7.17-7.10 (1H, m, major + minor, ArH), 7.02 (1H, d, J = 2.3 Hz, major, ArH), 6.97 (1H, d, J = 2.3 Hz, minor, ArH), 5.85-5.60 (1H, br. s, major + minor, C(O)NH), 3.63 (2H, app. q, J = 6.5 Hz, major, NHCH₂), 3.49 (2H, app. q, J = 6.5 Hz, minor, NHCH₂), 2.99 (2H, t, J = 6.7 Hz, major, CCH₂), 2.94 (2H, t, J = 6.4 Hz, minor, CCH₂); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_{C} = 164.8 (m), 161.5 (M), 136.6 (m), 136.5 (M), 127.3 (M), 126.9 (m), 122.9 (m), 122.4 (M), 122.3 (m), 122.2 (M), 119.6 (m), 119.5 (M), 118.7 (M), 118.4 (m), 112.4 (M), 111.6 (m), 111.5 (M), 111.4 (m), 42.1 (m), 38.4 (M), 27.4 (m), 25.2 (M); **IR** (neat): ν (cm⁻¹) = 3387, 3276 (N-H), 1652 (C=O); **HRMS** (ESI-TOF): m/z found 211.0849, C₁₁H₁₂N₂O [M+Na]⁺ requires 211.0847.

Spectroscopic data was found to be consistent with that reported within the literature.^{775,776}

***N*-(Diphenylmethyl)formamide (541)**



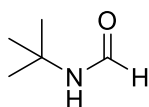
Benzhydrylamine (0.345 mL, 2 mmol) was subjected to general procedure **23a** and purification by flash column chromatography (eluent: CH₂Cl₂:EtOAc 80:20) afforded the title compound (0.351 g, 83%) as an off-white, crystalline solid; **mp** 133-134 °C (lit. 132-134 °C).⁷⁷⁷

Two rotamers were observed within the NMR spectra in an 84:16 ratio.

¹H NMR (300 MHz, CDCl₃): δ_{H} = 8.33 (1H, s, major, C(O)H), 8.24 (1H, d, J = 11.9 Hz, minor, C(O)H), 7.41-7.20 (10H, m, major + minor, PhH), 6.34 (1H, d, J = 8.1 Hz, major, NHCH), 6.21-6.04 (1H, br. s, major + minor, NH), 5.78 (1H, d, J = 8.3 Hz, minor, NHCH); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_{C} = 160.3 (M), 141.0 (M), 129.1 (m), 128.9 (M), 128.1 (m), 127.8 (M), 127.5 (M), 127.4 (m), 55.8 (M); **IR** (neat): ν (cm⁻¹) = 3184 (N-H), 1650 (C=O); **HRMS** (ESI-TOF): m/z found 234.0892, C₁₄H₁₃NO [M+Na]⁺ requires 234.0895.

Spectroscopic data was found to be consistent with that reported within the literature.^{778,779}

***N*-tert-Butylformamide (542)**



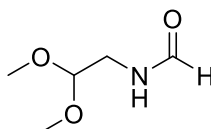
tert-Butylamine (0.210 mL, 2 mmol) was subjected to general procedure **23b** for 1 hour and purification by flash column chromatography (eluent: CH₂Cl₂:EtOAc 80:20) afforded the title compound (0.107 g, 53%) as a colourless oil.

Two rotamers were observed within the NMR spectra in a 51:49 ratio.

¹H NMR (300 MHz, CDCl₃): δ_H = 8.25 (1H, d, *J* = 12.4 Hz, major, C(O)H), 8.02 (1H, d, *J* = 1.7 Hz, minor, C(O)H), 6.51-5.77 (1H, br. s, major, NH), 5.72-5.03 (1H, br. s, minor, NH), 1.37 (9H, s, minor, 3 x CH₃), 1.32 (9H, s, major, 3 x CH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_C = 163.1 (m), 160.7 (M), 51.5 (M), 50.5 (m), 31.0 (M), 29.0 (m); **IR** (neat): ν (cm⁻¹) = 3284 (N-H), 1660 (C=O); **HRMS** (ESI-TOF): *m/z* found 102.0927, C₅H₁₁NO [M+H]⁺ requires 102.0919.

Spectroscopic data was found to be consistent with that reported within the literature.^{773,780}

***N*-(2,2-Dimethoxyethyl)formamide (543)**



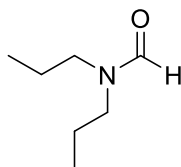
Aminoacetaldehyde dimethyl acetal (0.218 mL, 2 mmol) was subjected to general procedure **23a** and purification by flash column chromatography (eluent: CH₂Cl₂:EtOAc 80:20) afforded the title compound (0.253 g, 95%) as a pale yellow oil.

Two rotamers were observed within the NMR spectra in an 88:12 ratio.

¹H NMR (300 MHz, CDCl₃): δ_H = 8.20 (1H, s, major, C(O)H), 8.04 (1H, d, *J* = 12.0 Hz, minor, C(O)H), 5.94-5.57 (1H, br. s, major + minor, NH), 4.39 (1H, t, *J* = 5.2 Hz, major, CH₂CH), 4.32 (1H, t, *J* = 5.2 Hz, minor, CH₂CH), 3.48-3.43 (2H, m, major, CH₂), 3.41 (6H, s, minor, 2 x CH₃), 3.40 (6H, s, major, 2 x CH₃), 3.31 (2H, dd, *J* = 6.6, 5.2 Hz, minor, CH₂); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_C = 165.1 (m), 161.5 (M), 103.5 (m), 102.5 (M), 54.9 (m), 54.6 (M), 43.8 (m), 39.5 (M); **IR** (neat): ν (cm⁻¹) = 3295 (N-H), 1659 (C=O); **HRMS** (ESI-TOF): *m/z* found 134.0824, C₅H₁₁NO₃ [M+H]⁺ requires 134.0817.

Spectroscopic data was found to be consistent with that reported within the literature.⁷⁸¹

***N,N*-Dipropylformamide (544)**

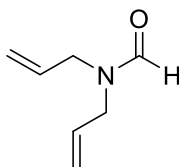


Dipropylamine (0.274 mL, 2 mmol) was subjected to general procedure **23a** and purification by flash column chromatography (eluent: CH₂Cl₂:EtOAc 80:20) afforded the title compound (0.192 g, 74%) as a very pale yellow liquid.

¹H NMR (300 MHz, CDCl₃): δ_H = 8.03 (1H, s, C(O)H), 3.26-3.19 (2H, m, NCH₂), 3.14 (2H, t, *J* = 7.1 Hz, NCH₂), 1.61-1.46 (4H, m, 2 x CH₃CH₂), 0.87 (3H, t, *J* = 7.4 Hz, CH₃), 0.86 (3H, t, *J* = 7.4 Hz, CH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_C = 162.9, 49.2, 43.8, 21.8, 20.6, 11.4, 11.0; **IR** (neat): ν (cm⁻¹) = 1660 (C=O); **HRMS** (ESI-TOF): *m/z* found 130.1245, C₇H₁₅NO [M+H]⁺ requires 130.1232.

Spectroscopic data was found to be consistent with that reported within the literature.^{782,783}

***N,N*-Bis(prop-2-en-1-yl)formamide (545)**

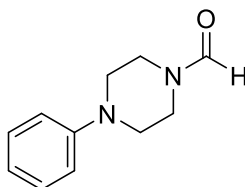


Diallylamine (0.247 mL, 2 mmol) was subjected to general procedure **23a** and purification by flash column chromatography (eluent: CH₂Cl₂:EtOAc 80:20) afforded the title compound (0.141 g, 56%) as a pale yellow oil.

¹H NMR (300 MHz, CDCl₃): δ_H = 8.13 (1H, s, C(O)H), 5.81-5.63 (2H, m, 2 x CH=CH₂), 5.27-5.20 (2H, m, 2 x CH=CH_AH_B), 5.20-5.12 (2H, m, 2 x CH=CH_AH_B), 3.94 (2H, dt, *J* = 6.0, 1.2 Hz, NCH₂), 3.82 (2H, dt, *J* = 5.8, 1.3 Hz, NCH₂); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_C = 162.6, 133.1, 132.1, 118.7, 118.2, 49.3, 44.3; **IR** (neat): ν (cm⁻¹) = 1666 (C=O); **HRMS** (ESI-TOF): *m/z* found 148.0752, C₇H₁₁NO [M+Na]⁺ requires 148.0738.

Spectroscopic data was found to be consistent with that reported within the literature.⁷⁸⁴

4-Phenylpiperazine-1-carbaldehyde (546)

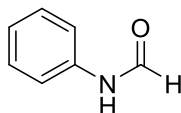


1-Phenylpiperazine (0.306 mL, 2 mmol) was subjected to general procedure **23a** and purification by flash column chromatography (eluent: CH₂Cl₂:EtOAc 70:30) afforded the title compound (0.365 g, 96%) as a pale pink, crystalline solid; **mp** 83-85 °C (lit. 84-85 °C).⁷⁸⁵

¹H NMR (300 MHz, CDCl₃): δ_{H} = 8.10 (1H, s, C(O)H), 7.33-7.26 (2H, m, PhH), 6.97-6.89 (3H, m, PhH), 3.74-3.69 (2H, m, NCH₂), 3.56-3.51 (2H, m, NCH₂), 3.22-3.12 (4H, m, 2 x NCH₂); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_{C} = 160.7, 150.9, 129.3, 120.8, 117.1, 50.4, 49.3, 45.5, 39.9; **IR** (neat): ν (cm⁻¹) = 1652 (C=O); **HRMS** (ESI-TOF): m/z found 213.1007, C₁₁H₁₄N₂O [M+Na]⁺ requires 213.1004.

Spectroscopic data was found to be consistent with that reported within the literature.^{785,786}

***N*-Phenylformamide (547)**



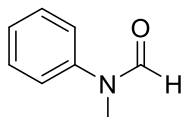
Aniline (0.182 mL, 2 mmol) was subjected to general procedure **23a** and purification by flash column chromatography (eluent: CH₂Cl₂:EtOAc 80:20) afforded the title compound (0.219 g, 90%) as a yellow oil.

Two rotamers were observed within the NMR spectra in a 51:49 ratio.

¹H NMR (300 MHz, CDCl₃): δ_{H} = 9.21-8.92 (1H, br. s, major, NH), 8.70 (1H, d, J = 11.3 Hz, major, C(O)H), 8.34 (1H, d, J = 1.6 Hz, minor, C(O)H), 8.30-8.04 (1H, br. s, minor, NH), 7.59-7.53 (1H, m, major + minor, PhH), 7.38-7.27 (2H, m, major + minor, PhH), 7.21-7.08 (2H, m, major + minor, PhH); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_{C} = 163.2 (M), 159.7 (m), 137.1 (m), 136.9 (M), 129.8 (M), 129.1 (m), 125.3 (M), 124.8 (m), 120.2 (m), 118.8 (M); **IR** (neat): ν (cm⁻¹) = 3265 (N-H), 1669 (C=O); **HRMS** (ESI-TOF): m/z found 144.0427, C₇H₇NO [M+Na]⁺ requires 144.0425.

Spectroscopic data was found to be consistent with that reported within the literature.^{591,787}

***N*-Methyl-*N*-phenylformamide (548)**



N-Methylaniline (0.217 mL, 2 mmol) was subjected to general procedure **23a** and purification by flash column chromatography (eluent: CH₂Cl₂:EtOAc 90:10) afforded the title compound (0.245 g, 91%) as a pale brown oil.

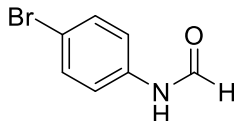
Two rotamers were observed within the NMR spectra in an 95:5 ratio.

¹H NMR (300 MHz, CDCl₃): δ_{H} = 8.48 (1H, s, major, C(O)H), 8.37 (1H, s, minor, C(O)H), 7.46-7.38 (2H, m, major + minor, PhH), 7.32-7.24 (1H, m, major + minor, PhH), 7.21-7.15 (2H, m,

major + minor, *PhH*), 3.36 (3H, s, minor, CH_3), 3.32 (3H, s, major, CH_3); $^{13}\text{C}\{^1\text{H}\}$ NMR (75.5 MHz, CDCl_3): δ_{C} = 162.3 (M), 162.2 (m), 142.0 (M), 129.5 (M), 128.9 (m), 126.3 (M), 126.1 (m), 123.5 (m), 122.2 (M), 36.8 (m), 31.9 (M); IR (neat): ν (cm^{-1}) = 1667 (C=O); HRMS (ESI-TOF): m/z found 136.0772, $\text{C}_8\text{H}_9\text{NO}$ $[\text{M}+\text{H}]^+$ requires 136.0762.

Spectroscopic data was found to be consistent with that reported within the literature.^{788,789}

***N*-(4-Bromophenyl)formamide (552)**



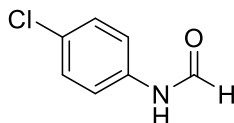
4-Bromoaniline (0.344 g, 2 mmol) was subjected to general procedure **23b** for 24 hours and purification by flash column chromatography (eluent: CH_2Cl_2 :EtOAc 85:15) afforded the title compound (0.382 g, 95%) as a white, crystalline solid; mp 115-117 °C (lit. 116-117 °C).⁷⁹⁰

Two rotamers were observed within the NMR spectra in an 61:39 ratio.

^1H NMR (300 MHz, CDCl_3): δ_{H} = 8.66 (1H, d, J = 11.3 Hz, minor, C(O)*H*), 8.38 (1H, d, J = 1.5 Hz, major, C(O)*H*), 8.18-8.01 (1H, br. d, minor, *NH*), 7.48 (2H, d, J = 8.8 Hz, minor, *ArH*), 7.45 (4H, app. s, major, *ArH*), 7.37-7.27 (1H, br. s, major, *NH*), 6.98 (2H, d, J = 8.8 Hz, minor, *ArH*); $^{13}\text{C}\{^1\text{H}\}$ NMR (75.5 MHz, CDCl_3): δ_{C} = 162.6 (m), 159.2 (M), 136.0 (M), 135.9 (m), 132.9 (m), 132.2 (M), 121.6 (M), 120.4 (m), 118.4 (m), 117.6 (M); IR (neat): ν (cm^{-1}) = 3253 (N-H), 1667 (C=O); HRMS (ESI-TOF): m/z found 199.9702, $\text{C}_7\text{H}_6\text{NOBr}$ $[\text{M}+\text{H}]^+$ requires 199.9711.

Spectroscopic data was found to be consistent with that reported within the literature.^{791,792}

***N*-(4-Chlorophenyl)formamide (553)**



4-Chloroaniline (0.255 g, 2 mmol) was subjected to general procedure **23b** for 24 hours and purification by flash column chromatography (eluent: CH_2Cl_2 :EtOAc 85:15) afforded the title compound (0.293 g, 94%) as a beige, crystalline solid; mp 101-102 °C (lit. 100-102 °C).⁷⁹³

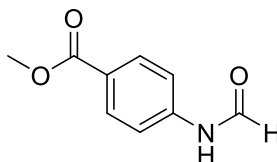
Two rotamers were observed within the NMR spectra in an 57:43 ratio.

^1H NMR (300 MHz, CDCl_3): δ_{H} = 8.87-8.71 (1H, br. d, minor, *NH*), 8.66 (1H, d, J = 11.2 Hz, minor, C(O)*H*), 8.37 (1H, d, J = 1.8 Hz, major, C(O)*H*), 7.92-7.71 (1H, br. s, major, *NH*), 7.51 (2H, d, J = 8.9 Hz, major, *ArH*), 7.33 (2H, d, J = 8.8 Hz, minor, *ArH*), 7.29 (2H, d, J = 9.0 Hz, major, *ArH*), 7.05 (2H, d, J = 8.8 Hz, minor, *ArH*); $^{13}\text{C}\{^1\text{H}\}$ NMR (75.5 MHz, CDCl_3): δ_{C} = 162.8

(m), 159.3 (M), 135.5 (M), 135.4 (m), 130.8 (M), 129.9 (m), 129.2 (M), 121.3 (M), 120.1 (m); **IR** (neat): ν (cm⁻¹) = 3257 (N-H), 1668 (C=O); **HRMS** (ESI-TOF): m/z found 178.0025, C₇H₆NOCl [M+Na]⁺ requires 178.0036.

Spectroscopic data was found to be consistent with that reported within the literature.^{791,792}

Methyl 4-formamidobenzoate (554)



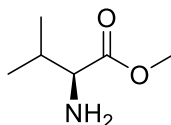
Methyl 4-aminobenzoate (0.302 g, 2 mmol) was subjected to general procedure **23b** for 24 hours and purification by flash column chromatography (eluent: CH₂Cl₂:EtOAc 85:15) afforded the title compound (0.311 g, 87%) as a white solid; **mp** 123-125 °C (lit. 123-125 °C).⁷⁹⁴

Two rotamers were observed within the NMR spectra in an 55:45 ratio.

¹H NMR (300 MHz, CDCl₃): δ_H = 8.86 (1H, d, J = 11.2 Hz, minor, C(O)H), 8.76-8.63 (1H, br. d, minor, NH), 8.43 (1H, d, J = 1.7 Hz, major, C(O)H), 8.03 (2H, d, J = 8.7 Hz, minor, ArH), 8.01 (2H, d, J = 8.7 Hz, major, ArH), 7.89-7.76 (1H, br. s, major, NH), 7.64 (2H, d, J = 8.8 Hz, major, ArH), 7.15 (2H, d, J = 8.7 Hz, minor, ArH), 3.91 (3H, s, minor, CH₃), 3.90 (3H, s, major, CH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_C = 166.6 (M), 166.4 (m), 162.1 (m), 159.2 (M), 141.1 (M), 141.0 (m), 131.7 (m), 131.0 (M), 126.7 (m), 126.3 (M), 119.2 (M), 117.3 (m), 52.4 (m), 52.3 (M); **IR** (neat): ν (cm⁻¹) = 3816 (N-H), 1694 (br., C=O formamide and ester); **HRMS** (ESI-TOF): m/z found 180.0649, C₉H₉NO₃ [M+H]⁺ requires 180.0661.

Spectroscopic data was found to be consistent with that reported within the literature.⁷⁹⁵

Methyl (2S)-2-amino-3-methylbutanoate (556)



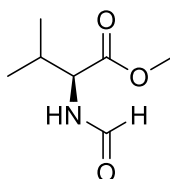
The following was based on a literature procedure published by Smith et al.⁶²¹ To a stirring suspension of L-valine (7.029 g, 60 mmol) in MeOH (42 mL) was added thionyl chloride (10.941 mL, 150 mmol, 2.5 equiv.) dropwise at 0 °C. The resulting solution was allowed to warm gradually to room temperature and was stirred for a further 4 hours. The reaction mixture was then concentrated to dryness *in vacuo*. The solid residue was then dissolved in EtOAc and washed 3 times with saturated aqueous NaHCO₃ solution before being dried over Na₂SO₄, filtered and

concentrated *in vacuo*. This afforded the title compound (1.341 g, 17%) cleanly as a very pale, yellow oil.

¹H NMR (250 MHz, CDCl₃): δ_H = 3.70 (3H, s, OCH₃), 3.28 (1H, d, *J* = 5.0 Hz, NH₂CH), 2.00 (1H, sept.d, *J* = 6.9, 5.0 Hz, CHCH₃), 1.53-1.35 (2H, br. s, NH₂), 0.95 (3H, d, *J* = 6.9 Hz, CHCH₃), 0.88 (3H, d, *J* = 6.9 Hz, CHCH₃).

Spectroscopic data was found to be consistent with that reported within the literature.⁷⁹⁶

Methyl (2S)-2-formamido-3-methylbutanoate (557)



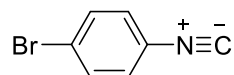
L-Valine methyl ester **556** (0.262 g, 2 mmol) was subjected to general procedure **23a** and purification by flash column chromatography (eluent: CH₂Cl₂:EtOAc 70:30) afforded the title compound (0.296 g, 93%) as a white, crystalline solid; **mp** 68-69 °C (lit. 72 °C).⁷⁹⁷

Two rotamers were observed within the NMR spectra in an 90:10 ratio.

¹H NMR (300 MHz, CDCl₃): δ_H = 8.22 (1H, s, major, C(O)H), 7.97 (1H, d, *J* = 11.7 Hz, minor, C(O)H), 6.70-6.30 (1H, br. m, major + minor, NH), 4.61 (1H, ddd, *J* = 9.1, 4.9, 0.7 Hz, major, NHCH), 3.90 (1H, dd, *J* = 10.2, 5.2 Hz, minor, NHCH), 3.73 (3H, s, minor, OCH₃), 3.71 (3H, s, major, OCH₃), 2.24-2.07 (1H, m, major + minor, CHCH₃), 0.94 (3H, d, *J* = 6.9 Hz, minor, CHCH₃), 0.92 (3H, d, *J* = 6.9 Hz, major, CHCH₃), 0.87 (3H, d, *J* = 6.9 Hz, major, CHCH₃), 0.87 (3H, d, *J* = 6.9 Hz, minor, CHCH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_C = 172.3 (M), 171.4 (m), 164.1 (m), 161.2 (M), 60.5 (m), 55.7 (M), 52.5 (m), 52.4 (M), 31.5 (m), 31.3 (M), 19.1 (m), 19.0 (M), 17.7 (M), 17.1 (m); **IR** (neat): ν (cm⁻¹) = 3207 (N-H), 1737 (C=O ester), 1646 (C=O formamide); **HRMS** (ESI-TOF): *m/z* found 160.0982, C₇H₁₃NO₃ [M+H]⁺ requires 160.0974; [α]_D²⁰ = -22 (*c* = 1.0, EtOH) [lit. [α]_D²⁰ = -23.73 (*c* = 2.0, EtOH)].⁵⁷³

Spectroscopic data was found to be consistent with that reported within the literature.^{524,579}

1-Bromo-4-isocyanobenzene (561)



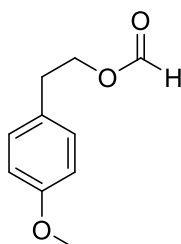
To a stirring solution of (formyloxy)(phenyl)methyl acetate **354** (0.583 g, 3 mmol, 1.5 equiv.) in CH₂Cl₂ (2 mL) was added 4-bromoaniline (0.344 g, 2 mmol) in a single portion. The reaction mixture was stirred for 24 hours at room temperature to generate *N*-(4-bromophenyl)formamide

552 *in situ*. Based on a literature procedure,^{623,624} the reaction was then placed under a nitrogen atmosphere, ⁱPr₂NH (1.121 mL, 8 mmol, 4.0 equiv.) was added and the mixture was cooled to 0 °C. POCl₃ (0.224 mL, 2.4 mmol, 1.2 equiv.) was then added dropwise and upon complete addition the reaction mixture was stirred at 0 °C for a further 2 hours. The reaction was slowly quenched with saturated aqueous Na₂CO₃ solution (0.8 g Na₂CO₃ in 4 mL H₂O), warmed to room temperature and left stirring vigorously for 12 hours. The resulting two layers were separated and the aqueous phase was extracted with CH₂Cl₂. The combined organic phases were washed with H₂O before being dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified using a short silica flash column (eluent: CH₂Cl₂) to afford the title compound (0.159 g, 44%) as a pale yellow solid; **mp** 96-97 °C (lit. 98 °C).⁷⁹⁰

¹H NMR (300 MHz, CDCl₃): δ_H = 7.53 (2H, d, *J* = 8.8 Hz, Ar*H*), 7.25 (2H, d, *J* = 8.6 Hz, Ar*H*); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_C = 165.7, 132.8, 127.9, 125.5 (m, C≡N), 123.5; **IR** (neat): ν (cm⁻¹) = 2122 (N≡C).

Spectroscopic data was found to be consistent with that reported within the literature.⁷⁹⁸

2-(4-Methoxyphenyl)ethyl formate (**565**)



(Formyloxy)(phenyl)methyl acetate **354** (0.583 g, 3 mmol, 1.5 equiv.), NaHCO₃ (0.336 g, 4 mmol, 2.0 equiv.) and 4-methoxyphenethyl alcohol (0.304 g, 2 mmol) were combined in a Radleys carousel tube. After sealing the tube, the resultant mixture was stirred and heated at 40 °C for 24 hours. The reaction was then allowed to cool to room temperature, diluted with CH₂Cl₂ and filtered to remove the NaHCO₃, before being concentrated *in vacuo*. The residue was then purified by flash column chromatography (eluent: Pentane:EtOAc 96:4) to afford the title compound (0.256 g, 71%) as a colourless oil.

¹H NMR (300 MHz, CDCl₃): δ_H = 8.04 (1H, s, C(O)*H*), 7.15 (2H, d, *J* = 8.7 Hz, 2 x OCCH*H*), 6.85 (2H, d, *J* = 8.7 Hz, 2 x OCCH), 4.35 (2H, td, *J* = 7.0, 0.7 Hz, OCH₂), 3.80 (3H, s, CH₃), 2.92 (2H, t, *J* = 7.0 Hz, OCH₂CH₂); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_C = 161.2, 158.5, 130.0, 129.5, 114.1, 64.8, 55.4, 34.2; **IR** (neat): ν (cm⁻¹) = 1718 (C=O); **HRMS** (ESI-TOF): *m/z* found 203.0687, C₁₀H₁₂O₃ [M+Na]⁺ requires 203.0684.

5.4 Experimental procedures and compound characterisation data for Chapter 4

5.4.1 General procedures for optimisation studies

Conversions were determined by analysis of the ^1H NMR spectra obtained in CDCl_3 for the crude reaction mixture. Specifically, for the bromination of *tert*-butylbenzene the conversion into **586** was determined by comparison of the integrals for the ^tBu signals of **585** and **586** at 1.37 ppm and 1.34 ppm respectively.

General procedure 24: *Catalyst investigations (Reactions performed in CDCl_3 , excluding solvent screen results)*

To a stirring mixture of *tert*-butylbenzene (0.310 mL, 2 mmol) and any specified catalyst and/or additive in CDCl_3 (2 mL) was added bromine in a single portion. The flask was then sealed and the resulting mixture was stirred at room temperature for the specified period of time. An aliquot of the reaction mixture was then removed for analysis by ^1H NMR spectroscopy.

Where specified, the reaction was also performed with the exclusion of light (Scheme 303)

Experimental procedure for the formation of an *N*-oxide bromine complex (Figure 72)

To a stirring mixture of 4-picoline *N*-oxide (0.022 g, 0.2 mmol) in CDCl_3 (2 mL) was added bromine (0.123 mL, 2.4 mmol, 12 equiv.) in a single portion. The flask was then sealed and the resulting mixture was stirred at room temperature for the specified period of time (5 min or 1 hour). An aliquot of the reaction mixture was then removed for analysis by ^1H NMR spectroscopy.

General procedure 25: *Reactions involving catalyst and bromine premixing (Schemes 302 and 310)*

To a stirring mixture of the appropriate catalyst (0.2 mmol, 10 mol%) in CDCl_3 (1.5 mL) was added bromine (0.123 mL, 2.4 mmol, 1.2 equiv.) in a single portion. The flask was then sealed and the resulting mixture was stirred for 30 minutes. *tert*-Butylbenzene (0.310 mL, 2 mmol) and additional CDCl_3 (0.5 mL) were then added and the reaction was left for a further 1 hour. After this period, an aliquot of the reaction mixture was removed for analysis by ^1H NMR spectroscopy.

General procedure 26: *Optimisation screens involving an aqueous work-up (Reactions performed in solvents other than CDCl_3)*

To a stirring mixture of *tert*-butylbenzene (0.310 mL, 2 mmol) and any specified catalyst in the appropriate solvent was added bromine in a single portion. The flask was then sealed and the

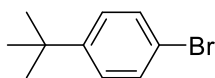
resulting mixture was stirred at room temperature for the specified time. After this period, 10% aqueous $\text{Na}_2\text{S}_2\text{O}_3$ solution was added to quench the unreacted bromine and an equal quantity of CH_2Cl_2 was added. The mixture was agitated until the organic phase became completely colourless and the resulting layers were then separated. The aqueous phase was extracted with a further portion of CH_2Cl_2 . The combined organic phases were washed two times with 10% aqueous $\text{Na}_2\text{S}_2\text{O}_3$ solution before being dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Conversions were determined by analysis of the ^1H NMR spectra obtained in CDCl_3 for the crude reaction mixture.

General procedure 27: Bromination of toluene (Table 48)

Where detailed, the reaction was performed with the exclusion of light. To a stirring mixture of toluene (0.213 mL, 2 mmol) and any specified catalyst (0.2 mmol, 10 mol%) in CDCl_3 (2 mL) was added bromine (1.2 or 2.0 equiv. as specified) in a single portion. The flask was then sealed and the resulting mixture was stirred at room temperature for 2 hours. An aliquot of the reaction mixture was then removed for analysis by ^1H NMR spectroscopy. The ratio of species present was determined by comparison of the integrals for the peaks at 2.30, 2.36, 2.40, 4.42, 4.49, 4.60, 6.57 and 6.64 ppm attributable to *p*-bromotoluene **589**, toluene **588**, *o*-bromotoluene **590**, *p*-bromobenzyl bromide **593**, benzyl bromide **591**, *o*-bromobenzyl bromide **594**, *p*-bromobenzyl dibromide **595** and benzyl dibromide **592** respectively.

5.4.2 Experimental Data

1-Bromo-4-(*tert*-butyl)benzene (586)



4-Picoline *N*-oxide catalysed bromination of 585:

To a stirring mixture of *tert*-butylbenzene (0.310 mL, 2 mmol) and 4-picoline *N*-oxide (0.022 g, 0.2 mmol, 10 mol%) in a 1:1 biphasic system of H₂O and CHCl₃ (1 mL total) was added bromine (0.205 mL, 4 mmol, 2.0 equiv.) in a single portion. The flask was then sealed and the resulting mixture was stirred at room temperature for 2 hours. After this period, 20% aqueous NaHSO₃ solution was added to quench the unreacted bromine and an equal quantity of CH₂Cl₂ was added. The mixture was agitated until the organic phase became completely colourless and the resulting layers were then separated. The aqueous phase was extracted with a further portion of CH₂Cl₂. The combined organic phases were washed twice with 20% aqueous NaHSO₃ solution before being dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude residue was triturated with pentane to precipitate the 4-picoline *N*-oxide and the liquor was then passed through a short silica plug to afford the title compound (0.409 g, 96%) as a colourless oil.

¹H NMR (300 MHz, CDCl₃): δ_H = 7.41 (2H, d, *J* = 8.8 Hz, 2 x BrCCH), 7.26 (2H, d, *J* = 8.8 Hz, 2 x BrCCHCH), 1.30 (9H, s, 3 x CH₃); **¹³C{¹H} NMR** (75.5 MHz, CDCl₃): δ_C = 150.3, 131.2, 127.3, 119.4, 34.7, 31.4; **IR** (neat): ν (cm⁻¹) = 2962, 2905, 2868 (C-H), 1493, 1476 (C=C aromatic); **GCMS** (EI): *t*_R = 7.614 min, *m/z* found 212.0201 (M⁺, 25), C₁₀H₁₃Br (M⁺) requires 212.0201.

Spectroscopic data was found to be consistent with that reported within the literature.⁶⁸⁹

Potassium iodide catalysed bromination of 585:

To a stirring mixture of *tert*-butylbenzene (0.310 mL, 2 mmol) and KI (0.033 g, 0.2 mmol, 10 mol%) in CH₂Cl₂ (1 mL) was added bromine (0.123 mL, 2.4 mmol, 1.2 equiv.) in a single portion. The flask was then sealed and the resulting mixture was stirred at room temperature for 2 hours. After this period, 20% aqueous NaHSO₃ solution was added to quench the unreacted bromine and an equal quantity of CH₂Cl₂ was added. The mixture was agitated until the organic phase became completely colourless and the resulting layers were then separated. The aqueous phase was extracted with a further portion of CH₂Cl₂. The combined organic phases were washed twice with 20% aqueous NaHSO₃ solution before being dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was then dissolved in pentane and passed through a silica plug, eluting with further pentane. The solution was then concentrated to dryness under reduced pressure to afford the title compound (0.376 g, 88%) as a colourless oil.

¹H NMR (500 MHz, CDCl₃): δ_H = 7.41 (2H, d, *J* = 8.3 Hz, 2 x BrCCH), 7.26 (2H, d, *J* = 8.3 Hz, 2 x BrCCHCH), 1.30 (9H, s, 3 x CH₃).

**6 Appendix: Single crystal X-ray diffraction data for
(1*S*,3*R*,6*R*,8*S*)-3,6-bis(4-methoxyphenyl)-1,8-dimethyl-2,7,9-trioxatricy-
clo[4.3.0.0^{3,8}]nonane (487)**

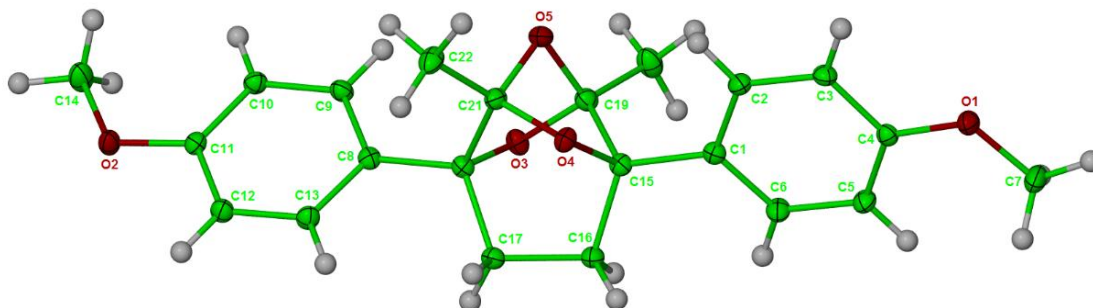


Figure 73. Molecular structure of (1*S*,3*R*,6*R*,8*S*)-3,6-bis(4-methoxyphenyl)-1,8-dimethyl-2,7,9-trioxatricyclo[4.3.0.0^{3,8}]nonane (487) obtained by single crystal X-ray diffraction. Thermal ellipsoids are shown at 30% probability.

Table 49. Crystal data and structure refinement for (1*S*,3*R*,6*R*,8*S*)-3,6-Bis(4-methoxyphenyl)-1,8-dimethyl-2,7,9-trioxatricyclo[4.3.0.0^{3,8}]nonane (**487**).

Identification code	k14sdb1
Empirical formula	C ₂₂ H ₂₄ O ₅
Formula weight	368.41
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2 ₁ /c
Unit cell dimensions	a = 10.5120(2) Å alpha = 90° b = 11.2520(2) Å beta = 106.107(1)° c = 16.4110(3) Å gamma = 90°
Volume	1864.91(6) Å ³
Z	4
Density (calculated)	1.312 Mg/m ³
Absorption coefficient	0.092 mm ⁻¹
F(000)	784
Crystal size	0.50 x 0.45 x 0.30 mm
Theta range for data collection	3.62 to 27.49°
Index ranges	-13 ≤ h ≤ 13; -14 ≤ k ≤ 14; -21 ≤ l ≤ 21
Reflections collected	35854
Independent reflections	4262 [R(int) = 0.0408]
Reflections observed (>2sigma)	3564
Data Completeness	0.997
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.960 and 0.901
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	4262 / 0 / 248
Goodness-of-fit on F ²	1.024
Final R indices [I > 2sigma(I)]	R1 = 0.0389 wR2 = 0.0959
R indices (all data)	R1 = 0.0485 wR2 = 0.1033
Largest diff. peak and hole	0.312 and -0.186 eÅ ⁻³

Table 50. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for (1*S*,3*R*,6*R*,8*S*)-3,6-bis(4-methoxyphenyl)-1,8-dimethyl-2,7,9-trioxatricyclo[4.3.0.0^{3,8}]nonane (**487**). U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

Atom	x	Y	z	U(eq)
O(1)	6044(1)	7159(1)	3283(1)	30(1)
O(2)	8925(1)	-3989(1)	6858(1)	31(1)
O(3)	7963(1)	554(1)	4496(1)	28(1)
O(4)	7295(1)	2574(1)	5512(1)	27(1)
O(5)	6081(1)	1228(1)	4665(1)	31(1)
C(1)	7295(1)	3829(1)	4313(1)	26(1)
C(2)	6070(1)	4318(1)	4313(1)	28(1)
C(3)	5678(1)	5417(1)	3954(1)	28(1)
C(4)	6498(1)	6054(1)	3574(1)	25(1)
C(5)	7689(1)	5565(1)	3532(1)	30(1)
C(6)	8078(1)	4460(1)	3905(1)	30(1)
C(7)	6808(2)	7826(1)	2851(1)	43(1)
C(8)	8392(1)	-603(1)	5786(1)	25(1)
C(9)	7604(1)	-1535(1)	5373(1)	28(1)
C(10)	7745(1)	-2682(1)	5706(1)	28(1)
C(11)	8691(1)	-2900(1)	6469(1)	25(1)
C(12)	9480(1)	-1975(1)	6894(1)	29(1)
C(13)	9329(1)	-841(1)	6556(1)	28(1)
C(14)	8178(2)	-4966(1)	6419(1)	43(1)
C(15)	7743(1)	2663(1)	4749(1)	25(1)
C(16)	9243(1)	2466(1)	5057(1)	27(1)
C(17)	9467(1)	1424(1)	5689(1)	27(1)
C(18)	8242(1)	626(1)	5413(1)	24(1)
C(19)	7058(1)	1511(1)	4242(1)	28(1)
C(20)	6546(2)	1573(1)	3299(1)	40(1)
C(21)	6963(1)	1346(1)	5498(1)	26(1)
C(22)	6363(1)	1028(1)	6194(1)	36(1)

Table 51. Bond lengths [Å] for (1*S*,3*R*,6*R*,8*S*)-3,6-Bis(4-methoxyphenyl)-1,8-dimethyl-2,7,9-trioxatricyclo[4.3.0.0^{3,8}]nonane (**487**).

Bond	Length (Å)	Bond	Length (Å)
O(1)-C(4)	1.3689(14)	O(1)-C(7)	1.4236(16)
O(2)-C(11)	1.3728(14)	O(2)-C(14)	1.4244(16)
O(3)-C(19)	1.4219(14)	O(3)-C(18)	1.4533(14)
O(4)-C(21)	1.4236(14)	O(4)-C(15)	1.4579(14)
O(5)-C(19)	1.4270(15)	O(5)-C(21)	1.4288(15)
C(1)-C(6)	1.3914(17)	C(1)-C(2)	1.4005(17)
C(1)-C(15)	1.5059(16)	C(2)-C(3)	1.3824(17)
C(3)-C(4)	1.3933(17)	C(4)-C(5)	1.3869(17)
C(5)-C(6)	1.3965(18)	C(8)-C(9)	1.3911(17)
C(8)-C(13)	1.3952(17)	C(8)-C(18)	1.5030(17)
C(9)-C(10)	1.3930(17)	C(10)-C(11)	1.3877(16)
C(11)-C(12)	1.3911(17)	C(12)-C(13)	1.3840(18)
C(15)-C(16)	1.5325(16)	C(15)-C(19)	1.6003(17)
C(16)-C(17)	1.5400(17)	C(17)-C(18)	1.5319(16)
C(18)-C(21)	1.6079(16)	C(19)-C(20)	1.4910(17)
C(21)-C(22)	1.4928(17)		

Table 52. Bond angles [°] for (1*S*,3*R*,6*R*,8*S*)-3,6-Bis(4-methoxyphenyl)-1,8-dimethyl-2,7,9-trioxatricyclo[4.3.0.0^{3,8}]nonane (**487**).

Bond	Angle (°)	Bond	Angle (°)
C(4)-O(1)-C(7)	117.61(10)	C(11)-O(2)-C(14)	116.79(10)
C(19)-O(3)-C(18)	100.82(8)	C(21)-O(4)-C(15)	100.89(8)
C(19)-O(5)-C(21)	94.66(8)	C(6)-C(1)-C(2)	117.80(11)
C(6)-C(1)-C(15)	121.65(11)	C(2)-C(1)-C(15)	120.55(10)
C(3)-C(2)-C(1)	121.09(11)	C(2)-C(3)-C(4)	120.20(11)
O(1)-C(4)-C(5)	125.04(11)	O(1)-C(4)-C(3)	115.14(10)
C(5)-C(4)-C(3)	119.81(11)	C(4)-C(5)-C(6)	119.35(11)
C(1)-C(6)-C(5)	121.65(11)	C(9)-C(8)-C(13)	118.20(11)
C(9)-C(8)-C(18)	120.93(10)	C(13)-C(8)-C(18)	120.88(11)
C(8)-C(9)-C(10)	121.52(11)	C(11)-C(10)-C(9)	119.28(11)
O(2)-C(11)-C(10)	124.65(11)	O(2)-C(11)-C(12)	115.39(10)
C(10)-C(11)-C(12)	119.96(11)	C(13)-C(12)-C(11)	120.14(11)
C(12)-C(13)-C(8)	120.91(11)	O(4)-C(15)-C(1)	109.59(9)
O(4)-C(15)-C(16)	104.78(9)	C(1)-C(15)-C(16)	116.11(10)
O(4)-C(15)-C(19)	100.67(9)	C(1)-C(15)-C(19)	114.97(9)
C(16)-C(15)-C(19)	109.11(9)	C(15)-C(16)-C(17)	106.48(10)
C(18)-C(17)-C(16)	106.71(9)	O(3)-C(18)-C(8)	109.78(9)
O(3)-C(18)-C(17)	104.51(9)	C(8)-C(18)-C(17)	115.71(10)
O(3)-C(18)-C(21)	100.66(9)	C(8)-C(18)-C(21)	115.10(10)
C(17)-C(18)-C(21)	109.48(9)	O(3)-C(19)-O(5)	101.59(9)
O(3)-C(19)-C(20)	111.07(10)	O(5)-C(19)-C(20)	114.48(11)
O(3)-C(19)-C(15)	107.03(9)	O(5)-C(19)-C(15)	102.01(9)
C(20)-C(19)-C(15)	118.91(11)	O(4)-C(21)-O(5)	101.36(9)
O(4)-C(21)-C(22)	111.92(10)	O(5)-C(21)-C(22)	114.13(10)
O(4)-C(21)-C(18)	106.49(9)	O(5)-C(21)-C(18)	101.93(9)
C(22)-C(21)-C(18)	119.10(10)		

Table 53. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for (1*S*,3*R*,6*R*,8*S*)-3,6-Bis(4-methoxyphenyl)-1,8-dimethyl-2,7,9-trioxatricyclo[4.3.0.0^{3,8}]nonane (**487**). The anisotropic displacement factor exponent takes the form: $-2 \text{ gpi}^2 [h^2 a^{*2} U11 + \dots + 2 h k a^* b^* U$

Atom	U11	U22	U33	U23	U13	U12
O(1)	29(1)	28(1)	35(1)	5(1)	10(1)	3(1)
O(2)	36(1)	25(1)	30(1)	2(1)	3(1)	-4(1)
O(3)	34(1)	27(1)	22(1)	-2(1)	5(1)	4(1)
O(4)	32(1)	24(1)	29(1)	0(1)	14(1)	0(1)
O(5)	23(1)	32(1)	37(1)	2(1)	4(1)	-2(1)
C(1)	26(1)	27(1)	24(1)	-1(1)	7(1)	0(1)
C(2)	24(1)	31(1)	30(1)	2(1)	9(1)	-2(1)
C(3)	21(1)	33(1)	30(1)	1(1)	8(1)	2(1)
C(4)	25(1)	26(1)	22(1)	-0(1)	4(1)	0(1)
C(5)	28(1)	32(1)	33(1)	4(1)	14(1)	0(1)
C(6)	27(1)	32(1)	35(1)	3(1)	14(1)	4(1)
C(7)	38(1)	36(1)	58(1)	17(1)	19(1)	2(1)
C(8)	25(1)	25(1)	25(1)	-1(1)	9(1)	2(1)
C(9)	25(1)	30(1)	26(1)	-1(1)	2(1)	-0(1)
C(10)	28(1)	27(1)	28(1)	-2(1)	6(1)	-4(1)
C(11)	27(1)	24(1)	25(1)	0(1)	10(1)	-1(1)
C(12)	32(1)	30(1)	23(1)	-0(1)	4(1)	-3(1)
C(13)	31(1)	26(1)	26(1)	-3(1)	5(1)	-4(1)
C(14)	51(1)	26(1)	43(1)	2(1)	-3(1)	-7(1)
C(15)	25(1)	27(1)	24(1)	-1(1)	10(1)	1(1)
C(16)	24(1)	29(1)	31(1)	1(1)	8(1)	0(1)
C(17)	24(1)	29(1)	28(1)	0(1)	6(1)	-0(1)
C(18)	26(1)	26(1)	22(1)	-2(1)	6(1)	1(1)
C(19)	27(1)	27(1)	29(1)	-0(1)	6(1)	1(1)
C(20)	49(1)	35(1)	30(1)	-1(1)	-2(1)	2(1)
C(21)	24(1)	24(1)	31(1)	0(1)	8(1)	0(1)
C(22)	37(1)	32(1)	46(1)	4(1)	23(1)	3(1)

Table 54. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for (1*S*,3*R*,6*R*,8*S*)-3,6-Bis(4-methoxyphenyl)-1,8-dimethyl-2,7,9-trioxatricyclo[4.3.0.0^{3,8}]nonane (**487**).

Atom	x	Y	z	U(eq)
H(2)	5499	3888	4564	34
H(3)	4848	5739	3966	33
H(5)	8235	5979	3252	36
H(6)	8898	4130	3879	36
H(7A)	7684	7988	3238	65
H(7B)	6358	8580	2655	65
H(7C)	6906	7372	2363	65
H(9)	6955	-1387	4851	34
H(10)	7200	-3308	5413	33
H(12)	10123	-2124	7419	35
H(13)	9870	-215	6852	34
H(14A)	7233	-4821	6344	65
H(14B)	8445	-5695	6748	65
H(14C)	8342	-5052	5862	65
H(16A)	9693	3190	5338	33
H(16B)	9597	2270	4574	33
H(17A)	10272	974	5678	33
H(17B)	9578	1722	6272	33
H(20A)	7279	1741	3056	61
H(20B)	5883	2206	3142	61
H(20C)	6139	811	3081	61
H(22A)	7043	1067	6740	54
H(22B)	6002	221	6103	54
H(22C)	5650	1589	6195	54

7 References

- (1) Bernier, D.; Wefelscheid, U. K.; Woodward, S. *Org. Prep. Proced. Int.* **2009**, *41*, 173.
- (2) Liu, X. H.; Lin, L. L.; Feng, X. M. *Acc. Chem. Res.* **2011**, *44*, 574.
- (3) Andreev, V. P. *Russ. J. Org. Chem.* **2009**, *45*, 1061.
- (4) Youssif, S. *Arkivoc* **2001**, 242.
- (5) Albini, A. *Synthesis Stuttgart* **1993**, 263.
- (6) Craig, J. C.; Purushot, K. K. *J. Org. Chem.* **1970**, *35*, 1721.
- (7) Albini, A.; Pietra, S. *Heterocyclic N-Oxides*; CRC Press: Florida, 1991.
- (8) Jacomb, R. G.; Brunnberg, F. J. *Clin. Sci. Mol. Med.* **1976**, *51*, S579.
- (9) Anthony, W. C.; Ursprung, J. J. *US Patent* **1969**, US3461461 A.
- (10) Selby, T. P.; Smith, B. T.; Stevenson, T. M. *World Intellectual Property Organisation* **2008**, WO2008100426 A2.
- (11) Rosenau, T.; Potthast, A.; Sixta, H.; Kosma, P. *Prog. Polym. Sci.* **2001**, *26*, 1763.
- (12) Wulfhorst, B.; Gries, T.; Veit, D. *Textile Technology*; Carl Hanser Verlag GmbH & Co. KG: Munich, 2006.
- (13) Cai, Y. F.; Liu, X. H.; Hui, Y. H.; Jiang, J.; Wang, W. T.; Chen, W. L.; Lin, L. L.; Feng, X. M. *Angew. Chem. Int. Ed.* **2010**, *49*, 6160.
- (14) Liang, L.; Li, Z. K.; Zhou, X. G. *Org. Lett.* **2009**, *11*, 3294.
- (15) Zhou, L.; Liu, X. H.; Ji, J.; Zhang, Y. H.; Hu, X. L.; Lin, L. L.; Feng, X. M. *J. Am. Chem. Soc.* **2012**, *134*, 17023.
- (16) Brandes, B. D.; Jacobsen, E. N. *J. Org. Chem.* **1994**, *59*, 4378.
- (17) Brandes, B. D.; Jacobsen, E. N. *Tetrahedron Lett.* **1995**, *36*, 5123.
- (18) Deng, L.; Jacobsen, E. N. *J. Org. Chem.* **1992**, *57*, 4320.
- (19) Jacobsen, E. N.; Deng, L.; Furukawa, Y.; Martinez, L. E. *Tetrahedron* **1994**, *50*, 4323.
- (20) Srinivasan, K.; Michaud, P.; Kochi, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 2309.
- (21) Santos, C. M. M.; Silva, A. M. S.; Cavaleiro, J. A. S.; Patonay, T.; Levai, A. *J. Heterocyclic Chem.* **2006**, *43*, 1319.
- (22) Chen, L. H.; Cheng, F. X.; Jia, L.; Wang, L.; Wei, J.; Zhang, J. F.; Yao, L. H.; Tang, N.; Wu, J. *C. Appl. Catal., A* **2012**, *415*, 40.
- (23) Irie, R.; Ito, Y.; Katsuki, T. *Synlett* **1991**, 265.
- (24) Sun, Y.; Tang, N. *J. Mol. Catal. A Chem.* **2006**, *255*, 171.
- (25) Kureshy, R. I.; Roy, T.; Khan, N. U.; Abdi, S. H. R.; Sadhukhan, A.; Bajaj, H. C. *J. Catal.* **2012**, *286*, 41.
- (26) Palucki, M.; McCormick, G. J.; Jacobsen, E. N. *Tetrahedron Lett.* **1995**, *36*, 5457.
- (27) Palucki, M.; Pospisil, P. J.; Zhang, W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1994**, *116*, 9333.
- (28) Senanayake, C. H.; Smith, G. B.; Ryan, K. M.; Fredenburgh, L. E.; Liu, J.; Roberts, F. E.; Hughes, D. L.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1996**, *37*, 3271.
- (29) Pietikainen, P. *Tetrahedron Lett.* **1994**, *35*, 941.
- (30) Kurti, L.; Blewett, M. M.; Corey, E. J. *Org. Lett.* **2009**, *11*, 4592.
- (31) Dalton, C. T.; Ryan, K. M.; Wall, V. M.; Bousquet, C.; Gilheany, D. G. *Top. Catal.* **1998**, *5*, 75.

References

- (32) Shen, J. K.; Gao, Y. C.; Shi, Q. Z.; Basolo, F. *Organometallics* **1989**, *8*, 2144.
- (33) Davies, J. A.; Hockensmith, C. M.; Kukushkin, V. Y.; Kukushkin, Y. N. *Synthetic Coordination Chemistry: Principles and Practice*; World Scientific Publishing Co. Pte. Ltd. : Singapore, 1996.
- (34) Alper, H.; Edward, J. T. *Can. J. Chem.* **1970**, *48*, 1543.
- (35) Shvo, Y.; Hazum, E. *J. Chem. Soc., Chem. Commun.* **1975**, 829.
- (36) Shvo, Y.; Hazum, E. *J. Chem. Soc., Chem. Commun.* **1974**, 336.
- (37) Shen, J. K.; Shi, Y. L.; Gao, Y. C.; Shi, Q. Z.; Basolo, F. *J. Am. Chem. Soc.* **1988**, *110*, 2414.
- (38) Knox, S. A. R.; McKinney, R. J.; Riera, V.; Stone, F. G. A.; Szary, A. C. *J. Chem. Soc., Dalton Trans.* **1979**, 1801.
- (39) Jeong, N.; Chung, Y. K.; Lee, B. Y.; Lee, S. H.; Yoo, S. E. *Synlett* **1991**, 204.
- (40) Kondo, T.; Yoshii, S.; Tsuji, Y.; Watanabe, Y. *J. Mol. Catal.* **1989**, *50*, 31.
- (41) Johnson, T. C.; Clarkson, G. J.; Wills, M. *Organometallics* **2011**, *30*, 1859.
- (42) Moyer, S. A.; Funk, T. W. *Tetrahedron Lett.* **2010**, *51*, 5430.
- (43) Kondo, T.; Kajiya, S.; Tantayanon, S.; Watanabe, Y. *J. Organomet. Chem.* **1995**, *489*, 83.
- (44) Zaitsev, A. B.; Adolfsson, H. *Synthesis Stuttgart* **2006**, 1725.
- (45) Vanrheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.
- (46) Parashar, R. K. *Reaction Mechanisms in Organic Synthesis*; John Wiley and Sons Ltd.: Chichester, UK, 2009.
- (47) Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968.
- (48) Balagam, B.; Mitra, R.; Richardson, D. E. *Tetrahedron Lett.* **2008**, *49*, 1071.
- (49) Ahrgren, L.; Sutin, L. *Org. Process Res. Dev.* **1997**, *1*, 425.
- (50) Andersson, M. A.; Eppele, R.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 472.
- (51) Lohray, B. B.; Kalantar, T. H.; Kim, B. M.; Park, C. Y.; Shibata, T.; Wai, J. S. M.; Sharpless, K. B. *Tetrahedron Lett.* **1989**, *30*, 2041.
- (52) Wang, Z. M.; Sharpless, K. B. *J. Org. Chem.* **1994**, *59*, 8302.
- (53) Crispino, G. A.; Jeong, K. S.; Kolb, H. C.; Wang, Z. M.; Xu, D. Q.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 3785.
- (54) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M.; Xu, D. Q.; Zhang, X. L. *J. Org. Chem.* **1992**, *57*, 2768.
- (55) Chandrasekhar, S.; Narsihmulu, C.; Sultana, S. S.; Reddy, N. R. *Chem. Commun.* **2003**, 1716.
- (56) Choi, D. S.; Han, S. S.; Kwueon, E. K.; Choi, H. Y.; Hwang, S. H.; Park, Y. S.; Song, C. E. *Adv. Synth. Catal.* **2006**, *348*, 2560.
- (57) Wai, J. S. M.; Marko, I.; Svendsen, J. S.; Finn, M. G.; Jacobsen, E. N.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 1123.
- (58) Choudary, B. M.; Chowdari, N. S.; Jyothi, K.; Kantam, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 5341.
- (59) Song, C. E.; Jung, D. U.; Roh, E. J.; Lee, S. G.; Chi, D. Y. *Chem. Commun.* **2002**, 3038.

- (60) Branco, L. C.; Afonso, C. A. M. *Chem. Commun.* **2002**, 3036.
- (61) Donohoe, T. J.; Wheelhouse, K. M. R.; Lindsay-Scott, P. J.; Glossop, P. A.; Nash, I. A.; Parker, J. S. *Angew. Chem. Int. Ed.* **2008**, *47*, 2872.
- (62) Donohoe, T. J.; Winship, P. C. M.; Tatton, M. R.; Szeto, P. *Angew. Chem. Int. Ed.* **2011**, *50*, 7604.
- (63) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis Stuttgart* **1994**, 639.
- (64) Moore, P. W.; Jiao, Y. X.; Mirzayans, P. M.; Sheng, L. N. Q.; Hooker, J. P.; Williams, C. M. *Eur. J. Org. Chem.* **2016**, 3401.
- (65) Moore, P. W.; Mirzayans, P. M.; Williams, C. M. *Chem. Eur. J.* **2015**, *21*, 3567.
- (66) Brown, D. S.; Kerr, W. J.; Lindsay, D. M.; Pike, K. G.; Ratcliffe, P. D. *Synlett* **2001**, 1257.
- (67) Schmidt, A. K. C.; Stark, C. B. W. *Org. Lett.* **2011**, *13*, 4164.
- (68) Roth, A. J.; Tretbar, M.; Stark, C. B. *Chem. Commun.* **2015**, *51*, 14175.
- (69) Sawama, Y.; Takubo, M.; Mori, S.; Monguchi, Y.; Sajiki, H. *Eur. J. Org. Chem.* **2011**, 3361.
- (70) Clayden, J.; Greeves, N.; Warren, S.; Wothers, P. *Organic Chemistry*; Oxford University Press Inc.: New York, 2001.
- (71) Andres, C. J.; Spetseris, N.; Norton, J. R.; Meyers, A. I. *Tetrahedron Lett.* **1995**, *36*, 1613.
- (72) Oh, K.; Ryu, J. *Tetrahedron Lett.* **2008**, *49*, 1935.
- (73) Schutznerova, E.; Krchnak, V. *J. Org. Chem.* **2016**, *81*, 3585.
- (74) Koster, R.; Arora, S.; Binger, P. *Angew. Chem. Int. Ed.* **1969**, *8*, 205.
- (75) Davies, A. G.; Roberts, B. P. *J. Chem. Soc. C* **1968**, 1474.
- (76) Soderquist, J. A.; Najafi, M. R. *J. Org. Chem.* **1986**, *51*, 1330.
- (77) Koster, R. *US Patent* **1971**, US3558633 A.
- (78) Aggarwal, V. K.; Fang, G. Y.; Ginesta, X.; Howells, D. M.; Zaja, M. *Pure Appl. Chem.* **2006**, *78*, 215.
- (79) Kabalka, G. W.; Hedgecock, H. C. *J. Org. Chem.* **1975**, *40*, 1776.
- (80) Bhat, N. G.; Varghese, N. *Synlett* **2007**, 2023.
- (81) Zhu, C.; Wang, R.; Falck, J. R. *Org. Lett.* **2012**, *14*, 3494.
- (82) Godfrey, A. G.; Ganem, B. *Tetrahedron Lett.* **1990**, *31*, 4825.
- (83) Chen, D. X.; Ho, C. M.; Wu, Q. Y. R.; Wu, P. R.; Wong, F. M.; Wu, W. M. *Tetrahedron Lett.* **2008**, *49*, 4147.
- (84) Barbry, D.; Champagne, P. *Tetrahedron Lett.* **1996**, *37*, 7725.
- (85) Mukaiyama, S.; Inanaga, J.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2221.
- (86) Khumraksa, B.; Phakhodee, W.; Pattarawarapan, M. *Tetrahedron Lett.* **2013**, *54*, 1983.
- (87) Beerappa, M.; Shivashankar, K. *Synth. Commun.* **2016**, *46*, 421.
- (88) Denmark, S. E.; Beutner, G. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 1560.
- (89) Malkov, A. V.; Ramirez-Lopez, P.; Biedermannova, L.; Rulisek, L.; Dufkova, L.; Kotora, M.; Zhu, F. J.; Kocovsky, P. *J. Am. Chem. Soc.* **2008**, *130*, 5341.
- (90) Chelucci, G.; Murineddu, G.; Pinna, G. A. *Tetrahedron: Asymmetry* **2004**, *15*, 1373.
- (91) Chelucci, G.; Baldino, S.; Pinna, G. A.; Benaglia, M.; Buffa, L.; Guizzetti, S. *Tetrahedron* **2008**, *64*, 7574.

- (92) Benaglia, M.; Guizzetti, S.; Pignataro, L. *Coord. Chem. Rev.* **2008**, 252, 492.
- (93) Malkov, A. V.; Kocovsky, P. *Eur. J. Org. Chem.* **2007**, 29.
- (94) Nakajima, M.; Saito, M.; Shiro, M.; Hashimoto, S. *J. Am. Chem. Soc.* **1998**, 120, 6419.
- (95) Hrdina, R.; Valterova, I.; Hodacova, J.; Cisarova, I.; Katora, M. *Adv. Synth. Catal.* **2007**, 349, 822.
- (96) Nakajima, M. *J. Syn. Org. Chem. Jpn.* **2003**, 61, 1081.
- (97) Simonini, V.; Benaglia, M.; Pignataro, L.; Guizzetti, S.; Celentano, G. *Synlett* **2008**, 1061.
- (98) Naicker, T.; Arvidsson, P. I.; Kruger, H. G.; Maguire, G. E. M.; Govender, T. *Eur. J. Org. Chem.* **2011**, 6923.
- (99) Hrdina, R.; Kadlcikova, A.; Valterova, I.; Hodacova, J.; Katora, M. *Tetrahedron: Asymmetry* **2006**, 17, 3185.
- (100) Orito, Y.; Nakajima, M. *Synthesis Stuttgart* **2006**, 1391.
- (101) Kocovsky, P.; Malkov, A. V. *Pure Appl. Chem.* **2008**, 80, 953.
- (102) Shimada, T.; Kina, A.; Hayashi, T. *J. Org. Chem.* **2003**, 68, 6329.
- (103) Traverse, J. F.; Zhao, Y.; Hoveyda, A. H.; Snapper, M. L. *Org. Lett.* **2005**, 7, 3151.
- (104) Chelucci, G.; Belmonte, N.; Benaglia, M.; Pignataro, L. *Tetrahedron Lett.* **2007**, 48, 4037.
- (105) Nakajima, M.; Saito, M.; Hashimoto, S. *Chem. Pharm. Bull.* **2000**, 48, 306.
- (106) Malkov, A. V.; Orsini, M.; Pernazza, D.; Muir, K. W.; Langer, V.; Meghani, P.; Kocovsky, P. *Org. Lett.* **2002**, 4, 1047.
- (107) Malkov, A. V.; Bell, M.; Orsini, M.; Pernazza, D.; Massa, A.; Herrmann, P.; Meghani, P.; Kocovsky, P. *J. Org. Chem.* **2003**, 68, 9659.
- (108) Kina, A.; Shimada, T.; Hayashi, T. *Adv. Synth. Catal.* **2004**, 346, 1169.
- (109) Malkov, A. V.; Dufkova, L.; Farrugia, L.; Kocovsky, P. *Angew. Chem. Int. Ed.* **2003**, 42, 3674.
- (110) Kadlcikova, A.; Hrdina, R.; Valterova, I.; Katora, M. *Adv. Synth. Catal.* **2009**, 351, 1279.
- (111) Vlasana, K.; Hrdina, R.; Valterova, I.; Katora, M. *Eur. J. Org. Chem.* **2010**, 7040.
- (112) Malkov, A. V.; Bell, M.; Castelluzzo, F.; Kocovsky, P. *Org. Lett.* **2005**, 7, 3219.
- (113) Malkov, A. V.; Bell, M.; Vassieu, M.; Bugatti, V.; Kocovsky, P. *J. Mol. Catal. A Chem.* **2003**, 196, 179.
- (114) Malkov, A. V.; Westwater, M. M.; Gutnov, A.; Ramirez-Lopez, P.; Friscourt, F.; Kadlcikova, A.; Hodacova, J.; Rankovic, Z.; Katora, M.; Kocovsky, P. *Tetrahedron* **2008**, 64, 11335.
- (115) Lu, T.; Porterfield, M. A.; Wheeler, S. E. *Org. Lett.* **2012**, 14, 5310.
- (116) Sepulveda, D.; Lu, T. X.; Wheeler, S. E. *Org. Biomol. Chem.* **2014**, 12, 8346.
- (117) Shimada, T.; Kina, A.; Ikeda, S.; Hayashi, T. *Org. Lett.* **2002**, 4, 2799.
- (118) Hrdina, R.; Opekar, F.; Roithova, J.; Katora, M. *Chem. Commun.* **2009**, 2314.
- (119) Hrdina, R.; Boyd, T.; Valterova, I.; Hodacova, J.; Katora, M. *Synlett* **2008**, 3141.
- (120) Hrdina, R.; Dracinsky, M.; Valterova, I.; Hodacova, J.; Cisarova, I.; Katora, M. *Adv. Synth. Catal.* **2008**, 350, 1449.
- (121) Kadlcikova, A.; Valterova, I.; Duchackova, L.; Roithova, J.; Katora, M. *Chem. Eur. J.* **2010**, 16, 9442.
- (122) Koukal, P.; Ulc, J.; Necas, D.; Katora, M. *Eur. J. Org. Chem.* **2016**, 2110.

- (123) Hessler, F.; Betik, R.; Kadlcikova, A.; Belle, R.; Kotora, M. *Eur. J. Org. Chem.* **2014**, 7245.
- (124) Motloch, P.; Valterova, I.; Kotora, M. *Adv. Synth. Catal.* **2014**, 356, 199.
- (125) Pignataro, L.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Celentano, G. *Chirality* **2005**, 17, 396.
- (126) Kwiatkowski, P.; Mucha, P.; Mloston, G.; Jurczak, J. *Synlett* **2009**, 1757.
- (127) Chai, Q.; Song, C.; Sun, Z. J.; Ma, Y. D.; Ma, C. Q.; Dai, Y.; Andrus, M. B. *Tetrahedron Lett.* **2006**, 47, 8611.
- (128) Pignataro, L.; Benaglia, M.; Annunziata, R.; Cinquini, M.; Cozzi, F. *J. Org. Chem.* **2006**, 71, 1458.
- (129) Wong, W. L.; Lee, C. S.; Leung, H. K.; Kwong, H. L. *Org. Biomol. Chem.* **2004**, 2, 1967.
- (130) Ikai, T.; Moro, M.; Maeda, K.; Kanoh, S. *React. Funct. Polym.* **2011**, 71, 1055.
- (131) Fulton, J. R.; Glover, J. E.; Kamara, L.; Rowlands, G. J. *Chem. Commun.* **2011**, 47, 433.
- (132) Muller, C. A.; Hoffart, T.; Holbach, M.; Reggelin, M. *Macromolecules* **2005**, 38, 5375.
- (133) Gnanamani, E.; Someshwar, N.; Sanjeevi, J.; Ramanathan, C. R. *Adv. Synth. Catal.* **2014**, 356, 2219.
- (134) Bai, B.; Shen, L.; Ren, J.; Zhu, H. J. *Adv. Synth. Catal.* **2012**, 354, 354.
- (135) Bai, B.; Zhu, H. J.; Pan, W. *Tetrahedron* **2012**, 68, 6829.
- (136) Deng, Y.; Pan, W.; Pei, Y. N.; Li, J. L.; Bai, B.; Zhu, H. J. *Tetrahedron* **2013**, 69, 10431.
- (137) Liu, L.; Yang, Q.; Yu, H.; Li, J. L.; Pei, Y. N.; Zhu, H. J.; Li, Z. Q.; Wang, X. K. *Tetrahedron* **2015**, 71, 3296.
- (138) Lu, T. X.; Zhu, R. X.; An, Y.; Wheeler, S. E. *J. Am. Chem. Soc.* **2012**, 134, 3095.
- (139) Kobayashi, S.; Nishio, K. *J. Am. Chem. Soc.* **1995**, 117, 6392.
- (140) Nakajima, M.; Saito, M.; Hashimoto, S. *Tetrahedron: Asymmetry* **2002**, 13, 2449.
- (141) Chen, J. S.; Captain, B.; Takenaka, N. *Org. Lett.* **2011**, 13, 1654.
- (142) Schneider, U.; Sugiura, M.; Kobayashi, S. *Adv. Synth. Catal.* **2006**, 348, 323.
- (143) Schneider, U.; Sugiura, M.; Kobayashi, S. *Tetrahedron* **2006**, 62, 496.
- (144) Nakajima, M.; Yokota, T.; Saito, M.; Hashimoto, S. *Tetrahedron Lett.* **2004**, 45, 61.
- (145) Denmark, S. E.; Fan, Y.; Eastgate, M. D. *J. Org. Chem.* **2005**, 70, 5235.
- (146) Denmark, S. E.; Fan, Y. *J. Am. Chem. Soc.* **2002**, 124, 4233.
- (147) Hagiwara, H.; Inoguchi, H.; Fukushima, M.; Hoshi, T.; Suzuki, T. *Synlett* **2005**, 2388.
- (148) Denmark, S. E.; Su, X. P.; Nishigaichi, Y. *J. Am. Chem. Soc.* **1998**, 120, 12990.
- (149) Acocella, M. R.; De Rosa, M.; Massa, A.; Palombi, L.; Villano, R.; Scettri, A. *Tetrahedron* **2005**, 61, 4091.
- (150) Scettri, A.; De Sio, V.; Villano, R.; Manzo, P.; Acocella, M. R. *Tetrahedron Lett.* **2010**, 51, 3658.
- (151) Nakajima, M.; Saito, M.; Uemura, M.; Hashimoto, S. *Tetrahedron Lett.* **2002**, 43, 8827.
- (152) Denmark, S. E.; Barsanti, P. A.; Wong, K. T.; Stavenger, R. A. *J. Org. Chem.* **1998**, 63, 2428.
- (153) Chen, J. S.; Takenaka, N. *Chem. Eur. J.* **2009**, 15, 7268.
- (154) Wang, P. A. *Beilstein J. Org. Chem.* **2013**, 9, 1677.
- (155) Denmark, S. E.; Barsanti, P. A.; Beutner, G. L.; Wilson, T. W. *Adv. Synth. Catal.* **2007**, 349, 567.

- (156) Tao, B.; Lo, M. M. C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 353.
- (157) Malkov, A. V.; Gordon, M. R.; Stoncius, S.; Hussain, J.; Kocovsky, P. *Org. Lett.* **2009**, *11*, 5390.
- (158) Neniskis, A.; Stoncius, S. *Eur. J. Org. Chem.* **2015**, 6359.
- (159) Takenaka, N.; Sarangthem, R. S.; Captain, B. *Angew. Chem. Int. Ed.* **2008**, *47*, 9708.
- (160) Yoshida, K.; Suzuki, H.; Inoue, H.; Matsui, K.; Fujino, Y.; Kanoko, Y.; Itatsu, Y.; Takao, K. *Adv. Synth. Catal.* **2016**, *358*, 1886.
- (161) Chen, F. X.; Zhou, H.; Liu, X. H.; Qin, B.; Feng, X. M.; Zhang, G. L.; Jiang, Y. Z. *Chem. Eur. J.* **2004**, *10*, 4790.
- (162) Shen, Y. C.; Feng, X. M.; Li, Y.; Zhang, G. L.; Jiang, Y. Z. *Synlett* **2002**, 793.
- (163) He, B.; Chen, F. X.; Li, Y.; Feng, X. M.; Zhang, G. L. *Eur. J. Org. Chem.* **2004**, 4657.
- (164) Kim, S. S.; Kim, D. W.; Rajagopal, G. *Synthesis Stuttgart* **2004**, 213.
- (165) Li, Q. H.; Liu, X. H.; Wang, J.; Shen, K.; Feng, X. M. *Tetrahedron Lett.* **2006**, *47*, 4011.
- (166) Liu, B.; Feng, X. M.; Chen, F. X.; Zhang, G. L.; Cui, X.; Jiang, Y. Z. *Synlett* **2001**, 1551.
- (167) Zhou, H.; Chen, F. X.; Qin, B.; Feng, Z. M.; Zhang, G. L. *Synlett* **2004**, 1077.
- (168) Denmark, S. E.; Chung, W. J. *J. Org. Chem.* **2006**, *71*, 4002.
- (169) Chen, F. X.; Feng, X. M. *Synlett* **2005**, 892.
- (170) Jiao, Z. G.; Feng, X. M.; Liu, B.; Chen, F. X.; Zhang, G. L.; Jiang, Y. Z. *Eur. J. Org. Chem.* **2003**, 3818.
- (171) Lv, C. W.; Cheng, Q. G.; Xu, D. Q.; Wang, S. F.; Xia, C. G.; Sun, W. *Eur. J. Org. Chem.* **2011**, 3407.
- (172) Chen, F. X.; Qin, B.; Feng, X. M.; Zhang, G. L.; Jiang, Y. Z. *Tetrahedron* **2004**, *60*, 10449.
- (173) Chen, F. X.; Liu, X. H.; Qin, B.; Zhou, H.; Feng, X. M.; Zhang, G. L. *Synthesis Stuttgart* **2004**, 2266.
- (174) Huang, J. L.; Liu, X. H.; Wen, Y. H.; Qin, B.; Feng, X. M. *J. Org. Chem.* **2007**, *72*, 204.
- (175) Qin, B.; Liu, X. H.; Shi, J.; Zheng, K.; Zhao, H. T.; Feng, X. M. *J. Org. Chem.* **2007**, *72*, 2374.
- (176) Khan, N. U. H.; Agrawal, S.; Kureshy, R. I.; Abdi, S. H. R.; Mayani, V. J.; Jasra, R. V. *Tetrahedron: Asymmetry* **2006**, *17*, 2659.
- (177) Shen, Y. C.; Feng, X. M.; Li, Y.; Zhang, G. L.; Jiang, Y. Z. *Tetrahedron* **2003**, *59*, 5667.
- (178) Kim, S. S.; Rajagopal, G.; Kim, D. W.; Song, D. H. *Synth. Commun.* **2004**, *34*, 2973.
- (179) Wen, Y. H.; Huang, X.; Huang, J. L.; Xiong, Y.; Qin, B.; Feng, X. M. *Synlett* **2005**, 2445.
- (180) Zeng, B. Q.; Zhou, X.; Liu, X. H.; Feng, X. M. *Tetrahedron* **2007**, *63*, 5129.
- (181) Prakash, G. K. S.; Mandal, M.; Panja, C.; Mathew, T.; Olah, G. A. *J. Fluorine Chem.* **2003**, *123*, 61.
- (182) Prakash, G. K. S.; Panja, C.; Vaghoo, H.; Surampudi, V.; Kultyshev, R.; Mandal, M.; Rasul, G.; Mathew, T.; Olah, G. A. *J. Org. Chem.* **2006**, *71*, 6806.
- (183) Shen, Y. C.; Feng, X. M.; Zhang, G. L.; Jiang, Y. Z. *Synlett* **2002**, 1353.
- (184) Shen, Y. C.; Feng, X. M.; Li, Y.; Zhang, G. L.; Jiang, Y. Z. *Eur. J. Org. Chem.* **2004**, 129.
- (185) Chen, F. X.; Feng, X. M.; Qin, B.; Zhang, G. L.; Jiang, Y. Z. *Org. Lett.* **2003**, *5*, 949.
- (186) He, B.; Chen, F. X.; Li, Y.; Feng, X. M.; Zhang, G. L. *Tetrahedron Lett.* **2004**, *45*, 5465.
- (187) Chen, F. X.; Feng, X. M.; Qin, B.; Zhang, G. L.; Jiang, Y. Z. *Synlett* **2003**, 558.

- (188) Li, Y.; He, B.; Feng, X. M.; Zhang, G. L. *Synlett* **2004**, 1598.
- (189) Wen, Y. H.; Gao, B.; Fu, Y. Z.; Dong, S. X.; Liu, X. H.; Feng, X. M. *Chem. Eur. J.* **2008**, *14*, 6789.
- (190) Huang, X.; Huang, J. L.; Wen, Y. H.; Feng, X. M. *Adv. Synth. Catal.* **2006**, *348*, 2579.
- (191) Hou, Z. R.; Wang, J.; Liu, X. H.; Feng, X. M. *Chem. Eur. J.* **2008**, *14*, 4484.
- (192) Pei, Y. N.; Deng, Y.; Li, J. L.; Liu, L.; Zhu, H. J. *Tetrahedron Lett.* **2014**, *55*, 2948.
- (193) Yoshida, K.; Takao, K. *Tetrahedron Lett.* **2014**, *55*, 6861.
- (194) Yoshida, K.; Fujino, Y.; Itatsu, Y.; Inoue, H.; Kanoko, Y.; Takao, K. *Tetrahedron Lett.* **2016**, *57*, 627.
- (195) Murray, J. I.; Spivey, A. C. *Adv. Synth. Catal.* **2015**, *357*, 3825.
- (196) Efimov, V. A.; Chakhmakhcheva, O. G. *Chem. Scripta* **1986**, *26*, 55.
- (197) Efimov, V. A.; Buryakova, A. A.; Dubey, I. Y.; Polushin, N. N.; Chakhmakhcheva, O. G.; Ovchinnikov, Y. A. *Nucleic Acids Res.* **1986**, *14*, 6525.
- (198) Efimov, V. A.; Chakhmakhcheva, O. G.; Ovchinnikov, Y. A. *Nucleic Acids Res.* **1985**, *13*, 3651.
- (199) Murray, J. I.; Woscholski, R.; Spivey, A. C. *Synlett* **2015**, *26*, 985.
- (200) Murray, J. I.; Woscholski, R.; Spivey, A. C. *Chem. Commun.* **2014**, *50*, 13608.
- (201) Shiina, I.; Kubota, M.; Ibuka, R. *Tetrahedron Lett.* **2002**, *43*, 7535.
- (202) Shiina, I.; Hashizume, M. *Tetrahedron* **2006**, *62*, 7934.
- (203) Shiina, I.; Hashizume, M.; Yamai, Y.; Oshiumi, H.; Shimazaki, T.; Takasuna, Y.; Ibuka, R. *Chem. Eur. J.* **2005**, *11*, 6601.
- (204) Shiina, I.; Kikuchi, T.; Sasaki, A. *Org. Lett.* **2006**, *8*, 4955.
- (205) Shiina, I.; Ushiyama, H.; Yamada, Y.; Kawakita, Y.; Nakata, K. *Chem. Asian. J.* **2008**, *3*, 454.
- (206) Ishihara, K.; Lu, Y. *Chem. Sci.* **2016**, *7*, 1276.
- (207) Klauber, E. G.; Mittal, N.; Shah, T. K.; Seidel, D. *Org. Lett.* **2011**, *13*, 2464.
- (208) Yang, Q.; Yin, Z. L.; Yang, M.; Peng, Y. Y. *Chin. J. Chem.* **2011**, *29*, 79.
- (209) Lin, Y. S.; Liu, C. W.; Tsai, T. Y. R. *Tetrahedron Lett.* **2005**, *46*, 1859.
- (210) Price, K. E.; Broadwater, S. J.; Walker, B. J.; McQuade, D. T. *J. Org. Chem.* **2005**, *70*, 3980.
- (211) Aggarwal, V. K.; Fulford, S. Y.; Lloyd-Jones, G. C. *Angew. Chem. Int. Ed.* **2005**, *44*, 1706.
- (212) Robiette, R.; Aggarwal, V. K.; Harvey, J. N. *J. Am. Chem. Soc.* **2007**, *129*, 15513.
- (213) Oh, K.; Li, J. Y.; Ryu, J. *Org. Biomol. Chem.* **2010**, *8*, 3015.
- (214) Oh, K.; Li, J. Y. *Synthesis Stuttgart* **2011**, 1960.
- (215) Bovonsombat, P.; Rujiwarangkul, R.; Bowornkiengkai, T.; Leykajarakul, J. *Tetrahedron Lett.* **2007**, *48*, 8607.
- (216) Cresswell, A. J.; Eey, S. T. C.; Denmark, S. E. *Nat. Chem.* **2015**, *7*, 146.
- (217) Egami, H.; Yoneda, T.; Uku, M.; Ide, T.; Kawato, Y.; Hamashima, Y. *J. Org. Chem.* **2016**, *81*, 4020.
- (218) Cai, Y. F.; Wang, W. T.; Shen, K.; Wang, J.; Hu, X. L.; Lin, L. L.; Liu, X. H.; Feng, X. M. *Chem. Commun.* **2010**, *46*, 1250.
- (219) Feng, J. H.; Fu, X.; Chen, Z. L.; Lin, L. L.; Liu, X. H.; Feng, X. M. *Org. Lett.* **2013**, *15*, 2640.
- (220) Feng, J. H.; Lin, L. L.; Yu, K. R.; Liu, X. H.; Feng, X. M. *Adv. Synth. Catal.* **2015**, *357*, 1305.

- (221) Wang, W.; Kumar, M.; Hammond, G. B.; Xu, B. *Org. Lett.* **2014**, *16*, 636.
- (222) Han, J. B.; Lu, Z. C.; Flach, A. L.; Paton, R. S.; Hammond, G. B.; Xu, B. *Chem. Eur. J.* **2015**, *21*, 11687.
- (223) Malhotra, D.; Hammond, G. B.; Xu, B.; Slaughter, L. M. *Homogeneous Gold Catalysis*; Springer: Cham, Switzerland, 2015.
- (224) BabaAhmadi, R.; Ghanbari, P.; Rajabi, N. A.; Hashmi, A. S. K.; Yates, B. F.; Ariafard, A. *Organometallics* **2015**, *34*, 3186.
- (225) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471.
- (226) Baeyer, A.; Villiger, V. *Ber. Dtsch. Chem. Ges.* **1899**, *32*, 3625.
- (227) Reyes, L.; Castro, M.; Cruz, J.; Rubio, M. *J. Phys. Chem. A* **2005**, *109*, 3383.
- (228) Renz, M.; Meunier, B. *Eur. J. Org. Chem.* **1999**, 737.
- (229) Schweitzer-Chaput, B.; Kurten, T.; Klussmann, M. *Angew. Chem. Int. Ed.* **2015**, *54*, 11848.
- (230) Alvarez-Idaboy, J. R.; Reyes, L.; Cruz, J. *Org. Lett.* **2006**, *8*, 1763.
- (231) Reyes, L.; Raul Alvarez-Idaboy, J.; Mora-Diez, N. *J. Phys. Org. Chem.* **2009**, *22*, 643.
- (232) Reyes, L.; Diaz-Sanchez, C.; Iuga, C. *J. Phys. Chem. A* **2012**, *116*, 7712.
- (233) Grein, F.; Chen, A. C.; Edwards, D.; Crudden, C. M. *J. Org. Chem.* **2006**, *71*, 861.
- (234) Michelin, R. A.; Sgarbossa, P.; Scarso, A.; Strukul, G. *Coord. Chem. Rev.* **2010**, *254*, 646.
- (235) Sever, R. R.; Root, T. W. *J. Phys. Chem. B* **2003**, *107*, 10521.
- (236) Kürti, L.; Czakó, B. *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier Academic Press: California, USA, 2005.
- (237) Leisch, H.; Morley, K.; Lau, P. C. *Chem. Rev.* **2011**, *111*, 4165.
- (238) Strukul, G. *Angew. Chem. Int. Ed.* **1998**, *37*, 1199.
- (239) Yakura, T.; Kitano, T.; Ikeda, M.; Uenishi, J. *Tetrahedron Lett.* **2002**, *43*, 6925.
- (240) Chen, C.; Peng, J.; Li, B.; Wang, L. *Catal. Lett.* **2009**, *131*, 618.
- (241) Jiménez-Sanchidrián, C.; Ruiz, J. R. *Tetrahedron* **2008**, *64*, 2011.
- (242) Krow, G. R. *Org. React.* **1993**, *43*, 251.
- (243) Yamabe, S.; Yamazaki, S. *J. Org. Chem.* **2007**, *72*, 3031.
- (244) Okuno, Y. *Chem. Eur. J.* **1997**, *3*, 212.
- (245) Chandler, C. L.; Phillips, A. J. *Org. Lett.* **2005**, *7*, 3493.
- (246) Jung, M. E.; Zeng, L. M.; Peng, T. S.; Zeng, H. Y.; Le, Y.; Su, J. Y. *J. Org. Chem.* **1992**, *57*, 3528.
- (247) Hagiwara, H.; Nagatomo, H.; Yoshii, F.; Hoshi, T.; Suzuki, T.; Ando, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2645.
- (248) Kane, V. V.; Doyle, D. L. *Tetrahedron Lett.* **1981**, *22*, 3031.
- (249) Laurent, M.; Ceresiat, M.; Marchand-Brynaert, J. *J. Org. Chem.* **2004**, *69*, 3194.
- (250) Deng, W.; Overman, L. E. *J. Am. Chem. Soc.* **1994**, *116*, 11241.
- (251) Ibrahim-Ouali, M.; Rocheblave, L. *Steroids* **2010**, *75*, 701.
- (252) Gan, C. F.; Cui, J. G.; Huang, Y. M.; Jia, L. Y.; Wei, W. X. *Steroids* **2012**, *77*, 255.
- (253) Siddiqui, A. U.; Satyanarayana, Y.; Ahmed, I.; Siddiqui, A. H. *Steroids* **1996**, *61*, 302.
- (254) Liu, Z. Y.; Ling, H.; Hu, Z. *Synlett* **1993**, 191.

- (255) Silk, P. J.; Ryall, K.; Mayo, P.; MaGee, D. I.; Leclair, G.; Fidgen, J.; Lavalley, R.; Price, J.; McConaghy, J. *J. Chem. Ecol.* **2015**, *41*, 294.
- (256) Ishmuratov, G. Y.; Yakovleva, M. P.; Valeeva, E. F.; Vydrina, V. A.; Tolstikov, G. A. *Russ. J. Bioorg. Chem.* **2012**, *38*, 667.
- (257) Sun, B.; Zhang, C. X.; Zhang, G. M.; Li, Y.; Li, Y. L.; Peng, L. Z. *Chin. J. Chem.* **2005**, *23*, 1228.
- (258) Boulton, L. T.; Brick, D.; Fox, M. E.; Jackson, M.; Lennon, I. C.; McCague, R.; Parkin, N.; Rhodes, D.; Ruecroft, G. *Org. Process Res. Dev.* **2002**, *6*, 138.
- (259) Li, N.; Chen, X. M.; Zhou, Y.; Wei, M. L.; Yao, X. *Clin. Exp. Ophthalmol.* **2006**, *34*, 755.
- (260) Weissermel, K.; Arpe, H.-J. *Industrial Organic Chemistry, Third Edition*; Wiley-VCH: Weinheim, Germany; New York, USA, 1997.
- (261) Bäckvall, J.-E. *Modern Oxidation Methods, Second Edition*; Wiley-VCH: Weinheim, Germany, 2010.
- (262) Sisson, A. L.; Ekinici, D.; Lendlein, A. *Polymer* **2013**, *54*, 4333.
- (263) Xian, M. *Sustainable Production of Bulk Chemicals*; Springer: Dordrecht, Netherlands, 2016.
- (264) Mislow, K.; Brenner, J. *J. Am. Chem. Soc.* **1953**, *75*, 2318.
- (265) Rozzell, J. D.; Benner, S. A. *J. Org. Chem.* **1983**, *48*, 1190.
- (266) Gallagher, T. F.; Kritchevsky, T. H. *J. Am. Chem. Soc.* **1950**, *72*, 882.
- (267) Turner, R. B. *J. Am. Chem. Soc.* **1950**, *72*, 878.
- (268) ten Brink, G. J.; Arends, I.; Sheldon, R. A. *Chem. Rev.* **2004**, *104*, 4105.
- (269) Tsunokawa, Y.; Iwasaki, S.; Okuda, S. *Chem. Pharm. Bull.* **1983**, *31*, 4578.
- (270) Imada, Y.; Iida, H.; Murahashi, S.; Naota, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 1704.
- (271) Zibuck, R.; Liverton, N. J.; Smith, A. B. *J. Am. Chem. Soc.* **1986**, *108*, 2451.
- (272) Krow, G. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Ley, S. V., Eds.; Elsevier Ltd.: Oxford, UK, 1991.
- (273) Grethe, G.; Sereno, J.; Williams, T. H.; Uskokovic, M. R. *J. Org. Chem.* **1983**, *48*, 5315.
- (274) Hannachi, H.; Anoune, N.; Arnaud, C.; Lanteri, P.; Longeray, R.; Chermette, H. *J. Mol. Struct. Theochem.* **1998**, *434*, 183.
- (275) Cardenas, R.; Cetina, R.; LagunezOtero, J.; Reyes, L. *J. Phys. Chem. A* **1997**, *101*, 192.
- (276) Doering, W. V.; Dorfman, E. *J. Am. Chem. Soc.* **1953**, *75*, 5595.
- (277) Doering, W. V.; Speers, L. *J. Am. Chem. Soc.* **1950**, *72*, 5515.
- (278) Crudden, C. M.; Chen, A. C.; Calhoun, L. A. *Angew. Chem. Int. Ed.* **2000**, *39*, 2851.
- (279) Palmer, B. W.; Fry, A. *J. Am. Chem. Soc.* **1970**, *92*, 2580.
- (280) Alvarez-Idaboy, J. R.; Reyes, L.; Mora-Diez, N. *Org. Biomol. Chem.* **2007**, *5*, 3682.
- (281) Bach, R. D. *J. Org. Chem.* **2012**, *77*, 6801.
- (282) Stoute, V. A.; Winnik, M. A.; Csizmadi, I. *J. Am. Chem. Soc.* **1974**, *96*, 6388.
- (283) Phillips, B.; Frostick, F. C.; Starcher, P. S. *J. Am. Chem. Soc.* **1957**, *79*, 5982.
- (284) Criegee, R. *Liebigs Ann. Chem.* **1948**, *560*, 127.
- (285) Winnik, M. A.; Stoute, V.; Fitzgerald, P. *J. Am. Chem. Soc.* **1974**, *96*, 1977.
- (286) Bunton, C. A.; Lewis, T. A.; Llewellyn, D. R. *J. Chem. Soc.* **1956**, 1226.

References

- (287) Berson, J. A.; Suzuki, S. *J. Am. Chem. Soc.* **1959**, *81*, 4088.
- (288) Jenner, G. *Tetrahedron Lett.* **2001**, *42*, 8969.
- (289) Singleton, D. A.; Szymanski, M. J. *J. Am. Chem. Soc.* **1999**, *121*, 9455.
- (290) Cadenas, R.; Reyes, L.; Lagunez-Otero, J.; Cetina, R. *J. Mol. Struct. Theochem.* **2000**, *497*, 211.
- (291) Reyes, L.; Alvarez-Idaboy, J. R.; Mora-Diez, N. *J. Phys. Org. Chem.* **2009**, *22*, 643.
- (292) Liu, B.; Meng, X. G.; Li, W. Y.; Zhou, L. C.; Hu, C. W. *J. Phys. Chem. A* **2012**, *116*, 2920.
- (293) Emmons, W. D.; Lucas, G. B. *J. Am. Chem. Soc.* **1955**, *77*, 2287.
- (294) Hawthorne, M. F.; Emmons, W. D.; McCallum, K. S. *J. Am. Chem. Soc.* **1958**, *80*, 6393.
- (295) Friess, S. L.; Soloway, A. H. *J. Am. Chem. Soc.* **1951**, *73*, 3968.
- (296) Yang, N.; Su, Z. S.; Feng, X. M.; Hu, C. W. *Chem. Eur. J.* **2015**, *21*, 7264.
- (297) Ogata, Y.; Sawaki, Y. *J. Org. Chem.* **1972**, *37*, 2953.
- (298) Goodman, R. M.; Kishi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 9392.
- (299) Noyori, R.; Sato, T.; Kobayashi, H. *Tetrahedron Lett.* **1980**, *21*, 2569.
- (300) Chandrasekhar, S.; Roy, C. D. *J. Chem. Soc., Perkin Trans. 2* **1994**, 2141.
- (301) Noyori, R.; Kobayashi, H.; Sato, T. *Tetrahedron Lett.* **1980**, *21*, 2573.
- (302) Chandrasekhar, S.; Roy, C. D. *Tetrahedron Lett.* **1987**, *28*, 6371.
- (303) Itoh, Y.; Yamanaka, M.; Mikami, K. *J. Org. Chem.* **2013**, *78*, 146.
- (304) Itoh, Y.; Yamanaka, M.; Mikami, K. *Org. Lett.* **2003**, *5*, 4803.
- (305) Winnik, M. A.; Stoute, V. *Can. J. Chem.* **1973**, *51*, 2788.
- (306) Frisone, M. D.; Pinna, F.; Strukul, G. *Organometallics* **1993**, *12*, 148.
- (307) Balke, K.; Kadow, M.; Mallin, H.; Sass, S.; Bornscheuer, U. T. *Org. Biomol. Chem.* **2012**, *10*, 6249.
- (308) Carlqvist, P.; Eklund, R.; Brinck, T. *J. Org. Chem.* **2001**, *66*, 1193.
- (309) Whitesell, J. K.; Matthews, R. S.; Helbling, A. M. *J. Org. Chem.* **1978**, *43*, 784.
- (310) Ménová, P.; Kafka, F.; Dvořáková, H.; Gunnoo, S.; Šanda, M.; Cibulka, R. *Adv. Synth. Catal.* **2011**, *353*, 865.
- (311) Xu, H. J.; Zhu, F. F.; Shen, Y. Y.; Wan, X.; Feng, Y. S. *Tetrahedron* **2012**, *68*, 4145.
- (312) Zhang, Z. G.; Parra, L. P.; Reetz, M. T. *Chemistry* **2012**, *18*, 10160.
- (313) Bradley, T. D.; Dragan, A.; Tomkinson, N. C. O. *Tetrahedron* **2015**, *71*, 8155.
- (314) Xu, S.; Wang, Z.; Zhang, X.; Zhang, X.; Ding, K. *Angew. Chem. Int. Ed.* **2008**, *47*, 2840.
- (315) Xu, S. M.; Wang, Z.; Li, Y. X.; Zhang, X. M.; Wang, H. M.; Ding, K. L. *Chem. Eur. J.* **2010**, *16*, 3021.
- (316) Caspi, E.; Chang, Y. W.; Dorfman, R. I. *J. Med. Pharm. Chem.* **1962**, *91*, 714.
- (317) Olah, G. A.; Yamato, T.; Iyer, P. S.; Trivedi, N. J.; Singh, B. P.; Prakash, G. K. S. *Mater. Chem. Phys.* **1987**, *17*, 21.
- (318) Ibrahim-Ouali, M.; Botsi-Nkomendi, N.; Rocheblave, L. *Tetrahedron Lett.* **2010**, *51*, 93.
- (319) Berkessel, A.; Andreae, M. R. M. *Tetrahedron Lett.* **2001**, *42*, 2293.
- (320) Wacek, A. V.; Bézard, A. V. *Ber. Dtsch. Chem. Ges.* **1941**, 74.
- (321) Reyes, L.; Nicolas-Vazquez, I.; Mora-Diez, N.; Alvarez-Idaboy, J. R. *J. Org. Chem.* **2013**, *78*, 2327.

- (322) Sauers, R. R. *J. Am. Chem. Soc.* **1959**, *81*, 925.
- (323) Friess, S. L. *J. Am. Chem. Soc.* **1949**, *71*, 2571.
- (324) Friess, S. L.; Pinson, R. *J. Am. Chem. Soc.* **1952**, *74*, 1302.
- (325) Hawthorne, M. F.; Emmons, W. D. *J. Am. Chem. Soc.* **1958**, *80*, 6398.
- (326) Alvarez-Idaboy, J. R.; Reyes, L. *J. Org. Chem.* **2007**, *72*, 6580.
- (327) Mora-Diez, N.; Keller, S.; Alvarez-Idaboy, J. R. *Org. Biomol. Chem.* **2009**, *7*, 3682.
- (328) Poladura, B.; Martinez-Castaneda, A.; Rodriguez-Solla, H.; Llavona, R.; Concellon, C.; del Amo, V. *Org. Lett.* **2013**, *15*, 2810.
- (329) Zhang, X.; Ye, J.; Yu, L.; Shi, X.; Zhang, M.; Xu, Q.; Lautens, M. *Adv. Synth. Catal.* **2015**, 357, 955.
- (330) Cao, X. F.; Sun, S. N.; Peng, X. W.; Zhong, L. X.; Sun, R. C.; Jiang, D. *J. Agric. Food Chem.* **2013**, *61*, 2489.
- (331) Harrisson, S.; Liu, X.; Ollagnier, J.-N.; Coutelier, O.; Marty, J.-D.; Destarac, M. *Polymers* **2014**, *6*, 1437.
- (332) Cai, X.-Q.; Wang, N.; Lin, X.-F. *J. Mol. Catal. B Enzym.* **2006**, *40*, 51.
- (333) Hu, C. L.; Wang, N.; Zhang, W. W.; Zhang, S.; Meng, Y. F.; Yu, X. Q. *J. Biotechnol.* **2015**, *194*, 12.
- (334) Ni, Z.; Zhou, P.; Jin, X.; Lin, X. F. *Chem. Biol. Drug. Des.* **2011**, *78*, 301.
- (335) Wang, Y. F.; Lalonde, J. J.; Momongan, M.; Bergbreiter, D. E.; Wong, C. H. *J. Am. Chem. Soc.* **1988**, *110*, 7200.
- (336) Kawasaki, M.; Goto, M.; Kawabata, S.; Kometani, T. *Tetrahedron: Asymmetry* **2001**, *12*, 585.
- (337) Barbier, P.; Guise, S.; Huitorel, P.; Amade, P.; Pesando, D.; Briand, C.; Peyrot, V. *Life Sci.* **2001**, *70*, 415.
- (338) Paul, V. J.; Fenical, W. *Tetrahedron* **1984**, *40*, 3053.
- (339) Duh, C. Y.; El-Gamal, A. A. H.; Wang, S. K. *Tetrahedron Lett.* **2003**, *44*, 9321.
- (340) Bourdron, J.; Commeiras, L.; Barbier, P.; Bourgarel-Rey, V.; Pasquier, E.; Vanthuyne, N.; Hubaud, J. C.; Peyrot, V.; Parrain, J. L. *Bioorg. Med. Chem.* **2006**, *14*, 5540.
- (341) Banthorpe, D. V.; Bilyard, H. J.; Brown, G. D. *Phytochemistry* **1989**, *28*, 2109.
- (342) Grayer, R. J.; Eckert, M. R.; Veitch, N. C.; Kite, G. C.; Marin, P. D.; Kokubun, T.; Simmonds, M. S. J.; Paton, A. J. *Phytochemistry* **2003**, *64*, 519.
- (343) Yang, D.; Ding, S. X.; Huang, J. H.; Zhao, K. *Chem. Commun.* **2013**, *49*, 1211.
- (344) Ye, S. M.; Leong, W. K. *J. Organomet. Chem.* **2006**, *691*, 1117.
- (345) Nicks, F.; Aznar, R.; Sainz, D.; Muller, G.; Demonceau, A. *Eur. J. Org. Chem.* **2009**, 5020.
- (346) Chen, M. S.; White, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 1346.
- (347) Henderson, W. H.; Check, C. T.; Proust, N.; Stambuli, J. P. *Org. Lett.* **2010**, *12*, 824.
- (348) Mendelovici, M.; Glotter, E. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1735.
- (349) Payne, G. B.; Williams, P. H. *J. Org. Chem.* **1959**, *24*, 284.
- (350) Walton, H. M. *J. Org. Chem.* **1957**, *22*, 1161.
- (351) Pelletier, S. W.; Chang, C. W. J.; Iyer, K. N. *J. Org. Chem.* **1969**, *34*, 3477.
- (352) Abad, A.; Agullo, C.; Arno, M.; Cunat, A. C.; Zaragoza, R. J. *J. Org. Chem.* **1989**, *54*, 5123.

References

- (353) Chang, C. W. J.; Pelletier, S. W. *Tetrahedron Lett.* **1966**, 5483.
- (354) Levine, S. D. *Tetrahedron Lett.* **1965**, 2233.
- (355) Hassall, C. H. *Org. React.* **1957**, 9, 73.
- (356) Ahmad, M. S.; Moinuddin, G. *Indian J. Chem. B.* **1981**, 20, 811.
- (357) Ahmad, M. S.; Khan, I. A.; Pillai, N. K. *Tetrahedron* **1980**, 36, 2341.
- (358) Mushfiq, M.; Khan, A. R.; Shamim, A.; Rehman, R.; Sultanat *Synth. Commun.* **2010**, 40, 1508.
- (359) Montury, M.; Gore, J. *Tetrahedron* **1977**, 33, 2819.
- (360) Ijima, A.; Takahash.K *Chem. Pharm. Bull.* **1973**, 21, 215.
- (361) Yokoyama, T.; Izui, N. *Bull. Chem. Soc. Jpn.* **1965**, 38, 1501.
- (362) DeBoer, A.; Ellwanger, R. E. *J. Org. Chem.* **1974**, 39, 77.
- (363) Kocor, M.; Kurek, A.; Dabrowsk.J *Tetrahedron* **1969**, 25, 4257.
- (364) Gingerich, S. B.; Jennings, P. W. *J. Org. Chem.* **1983**, 48, 2606.
- (365) Ahmad, M. S.; Siddiqi, A. R. *Indian J. Chem. B.* **1978**, 16, 963.
- (366) Goodman, R. M.; Kishi, Y. *J. Org. Chem.* **1994**, 59, 5125.
- (367) Reignier, T.; de Berardinis, V.; Petit, J. L.; Mariage, A.; Hamze, K.; Duquesne, K.; Alphand, V. *Chem. Commun.* **2014**, 50, 7793.
- (368) Bes, M. T.; Villa, R.; Roberts, S. M.; Wan, P. W. H.; Willetts, A. *J. Mol. Catal. B Enzym.* **1996**, 1, 127.
- (369) Dhar, D. N.; Munjal, R. C. *Synthesis Stuttgart* **1973**, 542.
- (370) Yokoyama.T; Nohara, F. *Bull. Chem. Soc. Jpn.* **1965**, 38, 1498.
- (371) Weitz, E.; Scheffer, A. *Ber. Dtsch. Chem. Ges.* **1921**, 54, 2327.
- (372) Fujise, Y.; Fujiwara, K.; Ito, Y. *Chem. Lett.* **1988**, 1475.
- (373) Isoe, S.; Hyeon, S. B.; Ichikawa, H.; Katsumura, S.; Sakan, T. *Tetrahedron Lett.* **1968**, 53, 5561.
- (374) Boeseken, L.; Soeman, A. L. *Rec. Trav. Chim.* **1933**, 52, 874.
- (375) Boeseken, J.; Jacobs, J. *Rec. Trav. Chim.* **1936**, 55, 786.
- (376) Labows, J. N. *Tetrahedron Lett.* **1970**, 403.
- (377) Caspi, E.; Dorfman, R. I.; Chang, Y. W. *J. Med. Pharm. Chem.* **1962**, 5, 714.
- (378) Krafft, G. A.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1981**, 103, 5459.
- (379) Shono, T.; Matsumura, Y.; Hibino, K.; Miyawaki, S. *Tetrahedron Lett.* **1974**, 1295.
- (380) Handley, J. R.; Swigar, A. A.; Silverstein, R. M. *J. Org. Chem.* **1979**, 44, 2954.
- (381) Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. T. *Drug Discov. Today* **2007**, 12, 8.
- (382) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley-VCH: Weinheim, Germany, 2005.
- (383) Schowen, K. B.; Limbach, H. H.; Denisov, G. S.; Schowen, R. L. *BBA-Bioenergetics* **2000**, 1458, 43.
- (384) Berg, J. M.; Tymoczko, J. L.; Stryer, L. *Biochemistry, 5th Edition*; W. H. Freeman and Company: New York, USA, 2002.
- (385) Ishikita, H.; Saito, K. *J. R. Soc. Interface* **2014**, 11, 20130518.
- (386) Shylesh, S.; Hanna, D.; Gomes, J.; Krishna, S.; Canlas, C. G.; Head-Gordon, M.; Bell, A. T. *ChemCatChem* **2014**, 6, 1283.

- (387) Kirby, A. J. *Acid-Base Catalysis by Enzymes*; In: *Encyclopedia of Life Sciences*; John Wiley and Sons, Ltd.: Chichester, UK, 2010.
- (388) Kath-Schorr, S.; Wilson, T. J.; Li, N. S.; Lu, J.; Piccirilli, J. A.; Lilley, D. M. J. *J. Am. Chem. Soc.* **2012**, *134*, 16717.
- (389) Frey, P. A.; Whitt, S. A.; Tobin, J. B. *Science* **1994**, *264*, 1927.
- (390) Pihko, P. M. *Hydrogen Bonding in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2009.
- (391) Benedict, H.; Limbach, H. H.; Wehlan, M.; Fehlhhammer, W. P.; Golubev, N. S.; Janoschek, R. *J. Am. Chem. Soc.* **1998**, *120*, 2939.
- (392) Albert, A.; Serjeant, E. P. *The Determination of Ionization Constants, Third Edition*; Chapman and Hall: New York, USA, 1984.
- (393) Laurence, C.; Brameld, K. A.; Graton, J.; Le Questel, J.-Y.; Renault, E. *J. Med. Chem.* **2009**, *52*, 4073.
- (394) Laurence, C.; Berthelot, M. *Perspect. Drug Discov. Des.* **2000**, *18*, 39.
- (395) Baures, P. W.; Wiznycia, A.; Beatty, A. M. *Bioorg. Med. Chem.* **2000**, *8*, 1599.
- (396) Prezhdo, V. V.; Vashchenko, E. V.; Prezhdo, O. V.; Pushko, A. *J. Mol. Struct.* **1999**, *510*, 69.
- (397) Dega-Szafran, Z.; Szafran, M.; Sitkowski, J.; Stefaniak, L. *J. Phys. Org. Chem.* **1996**, *9*, 746.
- (398) Balevicius, V.; Aidas, K.; Svoboda, I.; Fuess, H. *J. Phys. Chem. A* **2012**, *116*, 8753.
- (399) Stare, J.; Hartl, M.; Daemen, L.; Eckert, J. *Acta Chim. Slov.* **2011**, *58*, 521.
- (400) Doslic, N.; Stare, J.; Mavri, J. *Chem. Phys.* **2001**, *269*, 59.
- (401) Hussain, H.; Al-Harrasi, A.; Green, I. R.; Ahmed, I.; Abbas, G.; Rehman, N. U. *RSC Adv.* **2014**, *4*, 12882.
- (402) Schmidt, B.; Berger, R. *Adv. Synth. Catal.* **2013**, *355*, 463.
- (403) Demizu, Y.; Yamagata, N.; Nagoya, S.; Sato, Y.; Doi, M.; Tanaka, M.; Nagasawa, K.; Okuda, H.; Kurihara, M. *Tetrahedron* **2011**, *67*, 6155.
- (404) Lehn, J.-M.; Riehl, J.-J. *Mol. Phys.* **1964**, *8*, 33.
- (405) Schenk, G. H. *Organic Functional Group Analysis: Theory and Development*; Pergamon Press Ltd.: London, UK, 1968.
- (406) Coldham, I. *Comprehensive Organic Functional Group Transformations* **1995**, *1*, 377.
- (407) Riehl, J.-J.; Fougerousse, A. *Bull. Soc. Chim. Fr.* **1968**, 4083.
- (408) Wang, L. B.; Nakamura, S.; Ito, Y.; Toru, T. *Tetrahedron: Asymmetry* **2004**, *15*, 3059.
- (409) Lehtinen, C.; Nevalainen, V.; Brunow, G. *Tetrahedron* **2001**, *57*, 4741.
- (410) Miyamoto, K.; Sei, Y.; Yamaguchi, K.; Ochiai, M. *J. Am. Chem. Soc.* **2009**, *131*, 1382.
- (411) Ahmad, M. S.; Ansari, I. A.; Saleem, K.; Moinuddin, G. *Indian J. Chem. B.* **1984**, *23*, 1110.
- (412) Mita, T.; Sugawara, M.; Hasegawa, H.; Sato, Y. *J. Org. Chem.* **2012**, *77*, 2159.
- (413) Syper, L. *Tetrahedron* **1987**, *43*, 2853.
- (414) Yi, B.; Yin, Y. Y.; Yi, Z. Q.; Zhou, W.; Liu, H. T.; Tan, N. Y.; Yang, H. *Tetrahedron Lett.* **2016**, *57*, 2320.
- (415) Marce, P.; Lynch, J.; Blacker, A. J.; Williams, J. M. J. *Chem. Commun.* **2016**, *52*, 1013.
- (416) Davis, R.; Lovelace, T. C.; Martinez, N. J.; Millar, A. *Catal. Lett.* **1995**, *31*, 307.
- (417) Gardner, J. N.; Katritzky, A. R. *J. Chem. Soc.* **1957**, 4375.

- (418) De Rycke, N.; Couty, F.; David, O. R. *Chem. Eur. J.* **2011**, *17*, 12852.
- (419) Spivey, A. C.; Arseniyadis, S. *Angew. Chem. Int. Ed.* **2004**, *43*, 5436.
- (420) Heinrich, M. R.; Klisa, H. S.; Mayr, H.; Steglich, W.; Zipse, H. *Angew. Chem. Int. Ed.* **2003**, *42*, 4826.
- (421) Kaljurand, I.; Kutt, A.; Soovali, L.; Rodima, T.; Maemets, V.; Leito, I.; Koppel, I. A. *J. Org. Chem.* **2005**, *70*, 1019.
- (422) Bunting, J. W.; Toth, A.; Heo, C. K. M.; Moors, R. G. *J. Am. Chem. Soc.* **1990**, *112*, 8878.
- (423) Lewis, N. A.; Marzilli, P. A.; Fronczek, F. R.; Marzilli, L. G. *Inorg. Chem.* **2014**, *53*, 11096.
- (424) Abou-Shehada, S.; Teasdale, M. C.; Bull, S. D.; Wade, C. E.; Williams, J. M. J. *ChemSusChem* **2015**, *8*, 1083.
- (425) Hunter, C. A. *Angew. Chem. Int. Ed.* **2004**, *43*, 5310.
- (426) V., A. E.; Dougherty, D. A. *Modern Physical Organic Chemistry*; University Science Books: Sausalito, California, USA, 2006.
- (427) Smallwood, I. M. *Handbook of organic solvent properties*; Arnold: UK, 1996.
- (428) Henderson, R. K.; Jimenez-Gonzalez, C.; Constable, D. J. C.; Alston, S. R.; Inglis, G. G. A.; Fisher, G.; Sherwood, J.; Binks, S. P.; Curzons, A. D. *Green Chem.* **2011**, *13*, 854.
- (429) Capello, C.; Fischer, U.; Hungerbuhler, K. *Green Chem.* **2007**, *9*, 927.
- (430) Goodman, J. F.; Robson, P.; Wilson, E. R. *Trans. Faraday Soc.* **1962**, *58*, 1846.
- (431) Bodige, S. G.; Zottola, M. A.; McKay, S. E.; Blackstock, S. C. *Mater. Res. Bull.* **1998**, 243.
- (432) Rubottom, G. M.; Gruber, J. M.; Boeckman, R. K.; Ramaiah, M.; Medwid, J. B. *Tetrahedron Lett.* **1978**, 4603.
- (433) Birman, V. B.; Li, X. M.; Han, Z. F. *Org. Lett.* **2007**, *9*, 37.
- (434) Ogata, Y.; Sawaki, Y. *J. Am. Chem. Soc.* **1972**, *94*, 4189.
- (435) Thomas, C.; Bibal, B. *Green Chem.* **2014**, *16*, 1687.
- (436) Bonduelle, C.; Martin-Vaca, B.; Cossio, F. P.; Bourissou, D. *Chem. Eur. J.* **2008**, *14*, 5304.
- (437) Dove, A. P. *Acs Macro Letters* **2012**, *1*, 1409.
- (438) Allen, C. L.; Chhatwal, A. R.; Williams, J. M. *Chem. Commun.* **2012**, 48, 666.
- (439) Charville, H.; Jackson, D. A.; Hodges, G.; Whiting, A.; Wilson, M. R. *Eur. J. Org. Chem.* **2011**, 2011, 5981.
- (440) Lemmerer, A.; Govindraj, S.; Johnston, M.; Motloun, X.; Savig, K. L. *CrystEngComm* **2015**, *17*, 3591.
- (441) Zhang, H.; Jin, S.; Wen, X.; Liu, B.; Fang, Y.; Zhang, Y.; Wang, D. *J. Mol. Struct.* **2015**, *1092*, 211.
- (442) Capasso, S.; Mazzarella, L. *Peptides* **1998**, *19*, 389.
- (443) Kadota, J.; Pavlovic, D.; Desvergne, J. P.; Bibal, B.; Peruch, F.; Deffieux, A. *Macromolecules* **2010**, *43*, 8874.
- (444) Coady, D. J.; Fukushima, K.; Horn, H. W.; Rice, J. E.; Hedrick, J. L. *Chem. Commun.* **2011**, 47, 3105.
- (445) Lu, N.; Chang, W. H.; Tu, W. H.; Li, C. K. *Chem. Commun.* **2011**, 47, 7227.
- (446) Vuluga, D.; Legros, J.; Crousse, B.; Bonnet-Delpon, D. *Chem. Eur. J.* **2010**, *16*, 1776.

- (447) Robinson, M. W. C.; Pillinger, K. S.; Mabbett, I.; Timms, D. A.; Graham, A. E. *Tetrahedron* **2010**, *66*, 8377.
- (448) Dong, D. J.; Li, H. H.; Tian, S. K. *J. Am. Chem. Soc.* **2010**, *132*, 5018.
- (449) Kang, B.; Kim, M.; Lee, J.; Do, Y.; Chang, S. *J. Org. Chem.* **2006**, *71*, 6721.
- (450) Zumbansen, K.; Doebling, A.; List, B. *Adv. Synth. Catal.* **2010**, *352*, 1135.
- (451) Saiz-Poseu, J.; Faraudo, J.; Figueras, A.; Alibes, R.; Busque, F.; Ruiz-Molina, D. *Chem. Eur. J.* **2012**, *18*, 3056.
- (452) de Paula, B. R. S.; Zampieri, D. S.; Rodrigues, J. A. R.; Moran, P. J. S. *Tetrahedron: Asymmetry* **2013**, *24*, 973.
- (453) Lefebvre, Y.; Revesz, C. *J. Med. Chem.* **1975**, *18*, 581.
- (454) Jain, A. K.; Srivastava, S. K.; Srivastava, S. D. *J. Indian Chem. Soc.* **1991**, *68*, 452.
- (455) Yamane, M.; Uera, K.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 477.
- (456) Benati, L.; Casarini, D.; Montecchi, P. C.; Spagnolo, P. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1113.
- (457) Liu, Y.; Yun, X. L.; Zhang-Negre, D.; Huang, J. H.; Du, Y. F.; Zhao, K. *Synthesis Stuttgart* **2011**, 2984.
- (458) Chen, C.-T.; Kao, J.-Q.; Salunke, S. B.; Lin, Y.-H. *Org. Lett.* **2011**, *13*, 26.
- (459) Friess, S. L.; Farnham, N. *J. Am. Chem. Soc.* **1950**, *72*, 5518.
- (460) Lansbury, P. T.; Macleay, R. E.; Peterson, J. O. *Tetrahedron Lett.* **1964**, 311.
- (461) Archer, R. M.; Hutchby, M.; Winn, C. L.; Fossey, J. S.; Bull, S. D. *Tetrahedron* **2015**, *71*, 8838.
- (462) Nishio, Y.; Kawazu, A.; Hirano, S.; Matsubara, H. *Tetrahedron* **2016**, *72*, 720.
- (463) Gaspa, S.; Porcheddu, A.; De Luca, L. *Org. Lett.* **2015**, *17*, 3666.
- (464) Katayev, D.; Matousek, V.; Koller, R.; Togni, A. *Org. Lett.* **2015**, *17*, 5898.
- (465) Kodama, S.; Hashidate, S.; Nomoto, A.; Yano, S.; Ueshima, M.; Ogawa, A. *Chem. Lett.* **2011**, *40*, 495.
- (466) Kobayashi, S.; Tanaka, H.; Amii, H.; Uneyama, K. *Tetrahedron* **2003**, *59*, 1547.
- (467) Ogata, Y.; Sawaki, Y. *J. Org. Chem.* **1969**, *34*, 3985.
- (468) Curci, R.; Diprete, R. A.; Modena, G. *J. Org. Chem.* **1970**, *35*, 740.
- (469) Foley, M. A.; Jamison, T. F. *Org. Process Res. Dev.* **2010**, *14*, 1177.
- (470) Liu, Q.; Ai, H.-M. *Synth. Commun.* **2012**, *42*, 3004.
- (471) Tran, K. V.; Bickar, D. *J. Org. Chem.* **2006**, *71*, 6640.
- (472) Sakakura, A.; Kawajiri, K.; Ohkubo, T.; Kosugi, Y.; Ishihara, K. *J. Am. Chem. Soc.* **2007**, *129*, 14775.
- (473) Geibel, I.; Christoffers, J. *Eur. J. Org. Chem.* **2016**, 918.
- (474) Siqueira, E. P.; Rodrigues, J. A. R.; Moran, P. J. S. *Tetrahedron: Asymmetry* **2001**, *12*, 847.
- (475) Bruckner, R.; Harmata, M. *Organic Mechanisms: Reactions, Stereochemistry and Synthesis* Springer: Berlin, Germany; Heidelberg, Germany 2010.
- (476) Kerr, W. J.; Morrison, A. J.; Pazicky, M.; Weber, T. *Org. Lett.* **2012**, *14*, 2250.
- (477) Tsuruga, T.; Ebizuka, Y.; Nakajima, J.; Chun, Y. T.; Noguchi, H.; Iitaka, Y.; Sankawa, U. *Tetrahedron Lett.* **1984**, *25*, 4129.

- (478) Tyvorskii, V. I.; Bobrov, D. N.; Kulinkovich, O. G.; Aelterman, W.; De Kimpe, N. *Tetrahedron* **2000**, *56*, 7313.
- (479) Ding, C. Y.; Wang, L. L.; Chen, H. J.; Wild, C.; Ye, N.; Ding, Y.; Wang, T. Z.; White, M. A.; Shen, Q.; Zhou, J. *Org. Biomol. Chem.* **2014**, *12*, 8442.
- (480) Fan, B. T.; Barbu, A.; Doucet, J. P. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1937.
- (481) Hurtley, A. E.; Cismesia, M. A.; Ischay, M. A.; Yoon, T. R. *Tetrahedron* **2011**, *67*, 4442.
- (482) Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635.
- (483) Trost, B. M.; Balkovec, J. M.; Mao, M. K. T. *J. Am. Chem. Soc.* **1986**, *108*, 4974.
- (484) Sato, B.; Muramatsu, H.; Miyauchi, M.; Hori, Y.; Takase, S.; Hino, M.; Hashimoto, S.; Terano, H. *J. Antibiot.* **2000**, *53*, 123.
- (485) Xiang, J.; He, W.; Wu, C.; Liang, Z.; Yan, D. *Synthesis* **2013**, *45*, 2605.
- (486) Cubero, I. I.; Lopez-Espinosa, M. T. P. *Carbohydr. Res.* **1986**, *154*, 71.
- (487) Bach, R. D.; Canepa, C.; Winter, J. E.; Blanchette, P. E. *J. Org. Chem.* **1997**, *62*, 5191.
- (488) Konoike, T.; Araki, Y.; Kanda, Y. *Tetrahedron Lett.* **1999**, *40*, 6971.
- (489) Philippo, C. M. G.; Vo, N. H.; Paquette, L. A. *J. Am. Chem. Soc.* **1991**, *113*, 2762.
- (490) Ko, K.; Nakano, K.; Watanabe, S.; Ichikawa, Y.; Kotsuki, H. *Tetrahedron Lett.* **2009**, *50*, 4025.
- (491) Campos, J. M.; Nunez, M. C.; Sanchez, R. M.; Gomez-Vidal, J. A.; Rodriguez-Gonzalez, A.; Banez, M.; Gallo, M. A.; Lacal, J. C.; Espinosa, A. *Bioorg. Med. Chem.* **2002**, *10*, 2215.
- (492) Fantin, G.; Fogagnolo, M.; Guerrini, A.; Medici, A.; Pedrini, P.; Fontana, S. *Tetrahedron: Asymmetry* **2001**, *12*, 2709.
- (493) Ogata, Y.; Sawaki, Y. *J. Am. Chem. Soc.* **1973**, *95*, 4687.
- (494) Wang, Y.; Chackalamannil, S.; Aubé, J. *J. Org. Chem.* **2000**, *65*, 5120.
- (495) Azman, A.; Koller, J.; Plesnicar, B. *J. Am. Chem. Soc.* **1979**, *101*, 1107.
- (496) Tan, E.; Ung, S.; Corbet, M. *Eur. J. Org. Chem.* **2016**, 1836.
- (497) Duczek, W.; Deutsch, J.; Vieth, S.; Niclas, H. J. *Synthesis Stuttgart* **1996**, 37.
- (498) Han, Y.; Cai, L. S. *Tetrahedron Lett.* **1997**, *38*, 5423.
- (499) Faraj, M. K. *US Patent* **1992**, US5155267 A.
- (500) Jo, Y.; Ju, J.; Choe, J.; Song, K. H.; Lee, S. *J. Org. Chem.* **2009**, *74*, 6358.
- (501) Daszkiewicz, Z.; Domanski, A.; Kyzioł, J. B. *Chem. Pap.* **1993**, *47*, 109.
- (502) Fu, P. P.; Boyer, J. H. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2246.
- (503) Arlt, D.; Klein, G. *US Patent* **1983**, US4419297 A.
- (504) Ugi, I.; Fetzer, U.; Eholzer, U.; Knapfer, H.; Offerman, K. *Angew. Chem. Int. Ed.* **1965**, *4*, 472.
- (505) Kobayashi, G.; Saito, T.; Kitano, Y. *Synthesis Stuttgart* **2011**, 3225.
- (506) Domling, A. *Chem. Rev.* **2006**, *106*, 17.
- (507) Nechaev, A. A.; Peshkov, A. A.; Peshkov, V. A.; Van der Eycken, E. V. *Synthesis Stuttgart* **2016**, *48*, 2280.
- (508) Downie, I. M.; Earle, M. J.; Heaney, H.; Shuhaibar, K. F. *Tetrahedron* **1993**, *49*, 4015.
- (509) Dhake, K. P.; Tambade, P. J.; Singhal, R. S.; Bhanage, B. M. *Green Chem. Lett. Rev.* **2011**, *4*, 151.
- (510) Jackson, A.; Methcohn, O. *J. Chem. Soc., Chem. Commun.* **1995**, 1319.

- (511) Kobayashi, K.; Nagato, S.; Kawakita, M.; Morikawa, O.; Konishi, H. *Chem. Lett.* **1995**, 575.
- (512) Kakehi, A.; Ito, S.; Hayashi, S.; Fujii, T. *Bull. Chem. Soc. Jpn.* **1995**, 68, 3573.
- (513) Chen, B. C.; Bednarz, M. S.; Zhao, R. L.; Sundeen, J. E.; Chen, P.; Shen, Z. Q.; Skoumbourdis, A. P.; Barrish, J. C. *Tetrahedron Lett.* **2000**, 41, 5453.
- (514) Deutsch, J.; Eckelt, R.; Kockritz, A.; Martin, A. *Tetrahedron* **2009**, 65, 10365.
- (515) Shirini, F.; Mazloumi, M.; Seddighi, M. *Res. Chem. Intermed.* **2016**, 42, 1759.
- (516) Neveux, M.; Bruneau, C.; Dixneuf, P. H. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1197.
- (517) Martinez, J.; Laur, J. *Synthesis Stuttgart* **1982**, 979.
- (518) Florsheimer, A.; Kula, M. R. *Monatsh. Chem.* **1988**, 119, 1323.
- (519) Sheehan, J. C.; Yang, D. D. H. *J. Am. Chem. Soc.* **1958**, 80, 1154.
- (520) Yamashiro, D.; Li, C. H. *J. Org. Chem.* **1973**, 38, 2594.
- (521) van Melick, J. E. W.; Wolters, E. T. M. *Synth. Commun.* **1972**, 2, 83.
- (522) Pettit, G. R.; Parent, K.; Kalnins, M. V.; Liu, T. M. H.; Thomas, E. G. *J. Org. Chem.* **1961**, 26, 2563.
- (523) Grant, H. G.; Summers, L. A. *Aust. J. Chem.* **1980**, 33, 613.
- (524) El Dine, T. M.; Evans, D.; Rouden, J.; Blanchet, J. *Chem. Eur. J.* **2016**, 22, 5894.
- (525) Forsch, R. A.; Rosowsky, A. *J. Org. Chem.* **1985**, 50, 2582.
- (526) Hett, R.; Fang, Q. K.; Gao, Y.; Wald, S. A.; Senanayake, C. H. *Org. Process Res. Dev.* **1998**, 2, 96.
- (527) Ma, G.; Zancanella, M.; Oyola, Y.; Richardson, R. D.; Smith, J. W.; Romo, D. *Org. Lett.* **2006**, 8, 4497.
- (528) Freer, R. J.; Day, A. R.; Muthukumaraswamy, N.; Pinon, D.; Wu, A.; Showell, H. J.; Becker, E. L. *Biochemistry* **1982**, 21, 257.
- (529) Kobayashi, S.; Nishio, K. *J. Org. Chem.* **1994**, 59, 6620.
- (530) Kobayashi, S.; Yasuda, M.; Hachiya, I. *Chem. Lett.* **1996**, 407.
- (531) Kaboudin, B.; Khodamorady, M. *Synlett* **2010**, 2905.
- (532) Padwa, A.; Heydt, H. *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations: Heteroatom analogues of aldehydes and ketones*; Georg Thieme Verlag: Stuttgart, 2004.
- (533) Bagno, A.; Kantlehner, W.; Scherr, O.; Vetter, J.; Ziegler, G. *Eur. J. Org. Chem.* **2001**, 2947.
- (534) Yang, D.; Jeon, H. B. *Bull. Korean Chem. Soc.* **2010**, 31, 1424.
- (535) Olah, G. A.; Ohannesian, L.; Arvanaghi, M. *Chem. Rev.* **1987**, 87, 671.
- (536) Majumdar, S.; De, J.; Hossain, J.; Basak, A. *Tetrahedron Lett.* **2013**, 54, 262.
- (537) Gerack, C. J.; McElwee-White, L. *Molecules* **2014**, 19, 7689.
- (538) Lachowicz, B. *Monatsh. Chem.* **1888**, 9, 695.
- (539) Blicke, F. F.; Lu, C. J. *J. Am. Chem. Soc.* **1952**, 74, 3933.
- (540) Habibi, D.; Sahebkhitiari, H.; Nasrollahzadeh, M.; Taghipour, A. *Lett. Org. Chem.* **2013**, 10, 209.
- (541) Wichelhaus, H. *Chem. Ber.* **1869**, 2, 115.
- (542) Clark, V. M.; Kalckar, H. M. *J. Chem. Soc.* **1950**, 1029.

References

- (543) Jung, S. H.; Ahn, J. H.; Park, S. K.; Choi, J. K. *Bull. Korean Chem. Soc.* **2002**, 23, 149.
- (544) Tornesello, A. L.; Sanseverino, M.; Buonaguro, F. M. *Molecules* **2016**, 21.
- (545) Waki, M.; Meienhofer, J. J. *Org. Chem.* **1977**, 42, 2019.
- (546) Chen, F. M. F.; Benoiton, N. L. *Synthesis Stuttgart* **1979**, 709.
- (547) De Luca, L.; Giacomelli, G.; Porcheddu, A.; Salaris, M. *Synlett* **2004**, 2570.
- (548) Kim, J. G.; Jang, D. O. *Synlett* **2010**, 2093.
- (549) Brahmachari, G.; Laskar, S. *Tetrahedron Lett.* **2010**, 51, 2319.
- (550) Yang, X. J.; Zhang, Y. S. *Res. Chem. Intermed.* **2013**, 39, 2843.
- (551) Bhojgowd, M. R. M.; Nizam, A.; Pasha, M. A. *Chin. J. Catal.* **2010**, 31, 518.
- (552) Lei, M.; Ma, L.; Hu, L. H. *Tetrahedron Lett.* **2010**, 51, 4186.
- (553) Bahrami, K.; Khodaei, M. M.; Targhan, H.; Arabi, M. S. *Tetrahedron Lett.* **2013**, 54, 5064.
- (554) Baghbanian, S. M.; Farhang, M. *J. Mol. Liq.* **2013**, 183, 45.
- (555) Kim, J. G.; Jang, D. O. *Synlett* **2010**, 1231.
- (556) Kim, J. G.; Jang, D. O. *Bull. Korean Chem. Soc.* **2010**, 31, 2989.
- (557) Shekhar, A. C.; Kurnar, A. R.; Sathaiah, G.; Paul, V. L.; Sridhar, M.; Rao, P. S. *Tetrahedron Lett.* **2009**, 50, 7099.
- (558) Hosseini-Sarvari, M.; Sharghi, H. *J. Org. Chem.* **2006**, 71, 6652.
- (559) Pathare, S. P.; Sawant, R. V.; Akamanchi, K. G. *Tetrahedron Lett.* **2012**, 53, 3259.
- (560) Das, V. K.; Devi, R. R.; Raul, P. K.; Thakur, A. J. *Green Chem.* **2012**, 14, 847.
- (561) Reddy, M. B. M.; Ashoka, S.; Chandrappa, G. T.; Pasha, M. A. *Catal. Lett.* **2010**, 138, 82.
- (562) Krishnakumar, B.; Swaminathan, M. *J. Mol. Catal. A Chem.* **2011**, 334, 98.
- (563) Ansari, M. I.; Hussain, M. K.; Yadav, N.; Gupta, P. K.; Hajela, K. *Tetrahedron Lett.* **2012**, 53, 2063.
- (564) Hong, M.; Xiao, G. M. *J. Fluorine Chem.* **2013**, 146, 11.
- (565) Habibi, D.; Rahmani, P.; Akbaripناه, Z. *J. Chem.* **2013**, Article ID 972960.
- (566) Habibi, D.; Nasrollahzadeh, M.; Sahebekhtiari, H. *J. Mol. Catal. A Chem.* **2013**, 378, 148.
- (567) Bahari, S.; Mohammadi-Aghdam, B.; Sajadi, S. M.; Zeidali, F. *Bull. Korean Chem. Soc.* **2012**, 33, 2251.
- (568) Tajbakhsh, M.; Alinezhad, H.; Nasrollahzadeh, M.; Karnali, T. A. *J. Colloid Interface Sci.* **2016**, 471, 37.
- (569) Das, B.; Krishnaiah, M.; Balasubramanyam, P.; Veeranjanyulu, B.; Kumar, D. N. *Tetrahedron Lett.* **2008**, 49, 2225.
- (570) Niknam, K.; Saberi, D. *Tetrahedron Lett.* **2009**, 50, 5210.
- (571) Gibson, H. W. *Chem. Rev.* **1969**, 69, 673.
- (572) Desai, B.; Danks, T. N.; Wagner, G. *Tetrahedron Lett.* **2005**, 46, 955.
- (573) Kotha, S.; Behera, M.; Khedkar, P. *Tetrahedron Lett.* **2004**, 45, 7589.
- (574) Reddy, P. G.; Kumar, G. D. K.; Baskaran, S. *Tetrahedron Lett.* **2000**, 41, 9149.
- (575) Strazzolini, P.; Giumanini, A. G.; Cauci, S. *Tetrahedron* **1990**, 46, 1081.
- (576) Nolte, R. J. M.; Vanzomeren, J. A. J.; Zwikker, J. W. *J. Org. Chem.* **1978**, 43, 1972.
- (577) Johannsen, F.; Jorgensen, A.; Pedersen, E. B. *Chem. Scripta* **1986**, 26, 347.

- (578) Krishnamurthy, S. *Tetrahedron Lett.* **1982**, 23, 3315.
- (579) Chancellor, T.; Morton, C. *Synthesis Stuttgart* **1994**, 1023.
- (580) Saidi, O.; Bamford, M. J.; Blacker, A. J.; Lynch, J.; Marsden, S. P.; Plucinski, P.; Watson, R. J.; Williams, J. M. J. *Tetrahedron Lett.* **2010**, 51, 5804.
- (581) Ortega, N.; Richter, C.; Glorius, F. *Org. Lett.* **2013**, 15, 1776.
- (582) Preedasuriyachai, P.; Kitahara, H.; Chavasiri, W.; Sakurai, H. *Chem. Lett.* **2010**, 39, 1174.
- (583) Sussfink, G.; Längenbahn, M.; Jenke, T. *J. Organomet. Chem.* **1989**, 368, 103.
- (584) Tlili, A.; Blondiaux, E.; Frogneux, X.; Cantat, T. *Green Chem.* **2015**, 17, 157.
- (585) Zhang, L.; Han, Z. B.; Zhao, X. Y.; Wang, Z.; Ding, K. L. *Angew. Chem. Int. Ed.* **2015**, 54, 6186.
- (586) Joseph, S.; Das, P.; Srivastava, B.; Nizar, H.; Prasad, M. *Tetrahedron Lett.* **2013**, 54, 929.
- (587) Suchy, M.; Elmehriki, A. A. H.; Hudson, R. H. E. *Org. Lett.* **2011**, 13, 3952.
- (588) Lebleu, T.; Kotsuki, H.; Maddaluno, J.; Legros, J. *Tetrahedron Lett.* **2014**, 55, 362.
- (589) Cochet, T.; Bellosta, V.; Greiner, A.; Roche, D.; Cossy, J. *Synlett* **2011**, 1920.
- (590) Akikusa, N.; Mitsui, K.; Sakamoto, T.; Kikugawa, Y. *Synthesis Stuttgart* **1992**, 1058.
- (591) Katritzky, A. R.; Chang, H. X.; Yang, B. Z. *Synthesis Stuttgart* **1995**, 503.
- (592) Human, J. P. E.; Mills, J. A. *J. Chem. Soc.* **1948**, 1457.
- (593) Maya, F.; Tour, J. M. *Tetrahedron* **2004**, 60, 81.
- (594) Schmidhammer, H.; Brossi, A. *Can. J. Chem.* **1982**, 60, 3055.
- (595) Casanova, J.; Werner, N. D.; Schuster, R. E. *J. Org. Chem.* **1966**, 31, 3473.
- (596) Moffat, J.; Newton, M. V.; Papenmeier, G. J. *J. Org. Chem.* **1962**, 27, 4058.
- (597) Barton, D. H. R.; Parekh, S. I.; Tajbakhsh, M.; Theodorakis, E. A.; Tse, C. L. *Tetrahedron* **1994**, 50, 639.
- (598) Lewin, A. H.; Szewczyk, J.; Wilson, J. W.; Carroll, F. I. *Tetrahedron* **2005**, 61, 7144.
- (599) Rostamnia, S.; Doustkhah, E. *J. Mol. Catal. A Chem.* **2016**, 411, 317.
- (600) Iranpoor, N.; Firouzabadi, H.; Jamalian, A. *Tetrahedron Lett.* **2005**, 46, 7963.
- (601) Wang, J. J.; Rosingana, M.; Discordia, R. P.; Soundararajan, N.; Polniaszek, R. *Synlett* **2001**, 1485.
- (602) Franzke, A.; Mattke, T.; Leschinski, J.; Abdallah, R.; Bock, M.; Baumann, R.; Stroefel, E. *US Patent* **2014**, US8680333 B2.
- (603) Sheshenev, A. E.; Boltukhina, E. V.; Hii, K. K. *Chem. Commun.* **2013**, 49, 3685.
- (604) Lunazzi, L.; Macciantelli, D. *Tetrahedron* **1985**, 41, 1991.
- (605) Ducray, R.; Jones, C. D.; Jung, F. H.; Simpson, I. *US Patent* **2010**, US20100105655 A1.
- (606) Maliszewskyj, R. J.; Turcotte, M. G.; Mitchell, J. A. *US Patent* **2004**, US6723877 B1.
- (607) Ishii, Y.; Takeno, M.; Kawasaki, Y.; Muromachi, A.; Nishiyama, Y.; Sakaguchi, S. *J. Org. Chem.* **1996**, 61, 3088.
- (608) Hill, D. R.; Hsiao, C. N.; Kurukulasuriya, R.; Wittenberger, S. J. *Org. Lett.* **2002**, 4, 111.
- (609) Yale, H. L. *J. Org. Chem.* **1971**, 36, 3238.
- (610) Kisfaludy, L.; Otvos, L. *Synthesis Stuttgart* **1987**, 510.
- (611) Deutsch, J.; Niclas, H. J. *Synth. Commun.* **1993**, 23, 1561.

References

- (612) Deutsch, J.; Duczek, W.; Niclas, H. J. *J. Prakt. Chem.* **1996**, 338, 488.
- (613) Blackburn, G. M.; Dodds, H. L. H. *J. Chem. Soc. B* **1971**, 826.
- (614) Nguyen, T. B.; Sorres, J.; Tran, M. Q.; Ermolenko, L.; Al-Mourabit, A. *Org. Lett.* **2012**, 14, 3202.
- (615) Schaufelberger, F.; Hu, L.; Ramstrom, O. *Chem. Eur. J.* **2015**, 21, 9776.
- (616) Fulmer, G. R.; Miller, A. J. M.; Sherden, N. H.; Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M.; Bercaw, J. E.; Goldberg, K. I. *Organometallics* **2010**, 29, 2176.
- (617) Abraham, R. J.; Mobli, M.; Smith, R. J. *Magn. Reson. Chem.* **2003**, 41, 26.
- (618) Aleiwi, B. A.; Mitachi, K.; Kurosu, M. *Tetrahedron Lett.* **2013**, 54, 2077.
- (619) Dupont, J.; Pfeffer, M. *Palladacycles: Synthesis, Characterization and Applications*; WILEY-VCH Verlag GmbH & Co. KGaA: Weinheim, 2008.
- (620) Uetrecht, J. P.; Trager, W. *Drug Metabolism: Chemical and Enzymatic Aspects*; CRC Press: Florida, USA, 2007.
- (621) Campbell, C. D.; Concellon, C.; Smith, A. D. *Tetrahedron: Asymmetry* **2011**, 22, 797.
- (622) Emsermann, J.; Kauh, U.; Opatz, T. *Mar. Drugs* **2016**, 14, 83.
- (623) Polisar, J. G.; Norton, J. R. *Tetrahedron* **2012**, 68, 10236.
- (624) Shabaan, S.; Ba, L. A.; Abbas, M.; Burkholz, T.; Denkert, A.; Gohr, A.; Wessjohann, L. A.; Sasse, F.; Weber, W.; Jacob, C. *Chem. Commun.* **2009**, 4702.
- (625) Komiotis, D.; Agelis, G.; Manta, S.; Tzioumaki, N.; Tsoukala, E.; Antonakis, K. *J. Carbohydr. Chem.* **2006**, 25, 441.
- (626) McGinty, D.; Letizia, C. S.; Api, A. M. *Food Chem. Toxicol.* **2012**, 50, S425.
- (627) Letizia, C. S.; Cocchiara, J.; Lalko, J.; Api, A. M. *Food Chem. Toxicol.* **2003**, 41, 995.
- (628) McGinty, D.; Letizia, C. S.; Api, A. M. *Food Chem. Toxicol.* **2012**, 50, S471.
- (629) Fox, M. A.; Whitesell, J. K. *Organic Chemistry, Third Edition*; Jones and Bartlett Publishers: Massachusetts, USA, 2004.
- (630) Voskressensky, L. G.; Golantsov, N. E.; Maharramov, A. M. *Synthesis Stuttgart* **2016**, 48, 615.
- (631) Gribble, G. W. *Chem. Soc. Rev.* **1999**, 28, 335.
- (632) Butler, A.; Walker, J. V. *Chem. Rev.* **1993**, 93, 1937.
- (633) Golantsov, N. E.; Festa, A. A.; Karchava, A. V.; Yurovskaya, M. A. *Chem. Heterocycl. Compd.* **2013**, 49, 203.
- (634) Skropeta, D. *Nat. Prod. Rep.* **2008**, 25, 1131.
- (635) Gribble, G. W. *Acc. Chem. Res.* **1998**, 31, 141.
- (636) Podgorsek, A.; Stavber, S.; Zupan, M.; Iskra, J. *Tetrahedron* **2009**, 65, 4429.
- (637) Andrievsky, A. M.; Gorelik, M. V. *Russ. Chem. Rev.* **2011**, 80, 421.
- (638) Adimurthy, S.; Ghosh, S.; Patoliya, P. U.; Ramachandraiah, G.; Agrawal, M.; Gandhi, M. R.; Upadhyay, S. C.; Ghosh, P. K.; Ranu, B. C. *Green Chem.* **2008**, 10, 232.
- (639) Vincent, S. H.; Shambhu, M. B.; Digenis, G. A. *J. Med. Chem.* **1980**, 23, 75.
- (640) Dagani, M. J.; Barda, H. J.; Benya, T. J.; Sanders, D. C. *Ullmann's Encyclopedia of Industrial Chemistry; Bromine Compounds*; Wiley-VCH: Weinheim, 2002.

- (641) Lomakin, S. M.; Zaikov, G. E. *New Concepts in Polymer Science: Modern Polymer Flame Retardancy*; VSP: Boston, 2003.
- (642) Sheppard, T. D. *Org. Biomol. Chem.* **2009**, *7*, 1043.
- (643) Seechurn, C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem. Int. Ed.* **2012**, *51*, 5062.
- (644) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337.
- (645) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428.
- (646) Goldbach, M.; Danieli, E.; Perlo, J.; Kaptein, B.; Litvinov, V. M.; Blumich, B.; Casanova, F.; Duchateau, A. L. L. *Tetrahedron Lett.* **2016**, *57*, 122.
- (647) Clayden, J. *Organolithiums: Selectivity for synthesis*; Pergamon: Amsterdam, Netherlands, 2002.
- (648) Bunnett, J. F.; Levitt, A. *J. Am. Chem. Soc.* **1948**, *70*, 2778.
- (649) Rajesh, K.; Somasundaram, M.; Saiganesh, R.; Balasubramanian, K. K. *J. Org. Chem.* **2007**, *72*, 5867.
- (650) Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 2523.
- (651) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4442.
- (652) Xiang, Y. Q.; Caron, P. Y.; Lillie, B. M.; Vaidyanathan, R. *Org. Process Res. Dev.* **2008**, *12*, 116.
- (653) Riva, E.; Gagliardi, S.; Martinelli, M.; Passarella, D.; Vigo, D.; Rencurosi, A. *Tetrahedron* **2010**, *66*, 3242.
- (654) Torborg, C.; Beller, M. *Adv. Synth. Catal.* **2009**, *351*, 3027.
- (655) de Vries, J. G. *Can. J. Chem.* **2001**, *79*, 1086.
- (656) Chaudhuri, S. K.; Roy, S.; Saha, M.; Bhar, S. *Synth. Commun.* **2007**, *37*, 579.
- (657) Eissen, M.; Lenoir, D. *Chem. Eur. J.* **2008**, *14*, 9830.
- (658) Khazaei, A.; Zolfigol, M. A.; Kolvari, E.; Koukabi, N.; Soltani, H.; Bayani, L. S. *Synth. Commun.* **2010**, *40*, 2954.
- (659) Cardinal, P.; Greer, B.; Luong, H.; Tyagunova, Y. *J. Chem. Educ.* **2012**, *89*, 1061.
- (660) Zhang, Q.; Gong, S. W.; Liu, L. J.; Yin, H. D. *Process Saf. Environ.* **2013**, *91*, 86.
- (661) Clark, J. H. *Green Chem.* **1999**, *1*, 1.
- (662) Groweiss, A. *Org. Process Res. Dev.* **2000**, *4*, 30.
- (663) Bovonsombat, P.; Ali, R.; Khan, C.; Leykajarakul, J.; Pla-on, K.; Aphimanchindakul, S.; Pungcharoenpong, N.; Timsuea, N.; Arunrat, A.; Punpongjareorn, N. *Tetrahedron* **2010**, *66*, 6928.
- (664) Rozen, S.; Lerman, O. *J. Org. Chem.* **1993**, *58*, 239.
- (665) Gupta, N.; Kad, G. L.; Singh, V.; Singh, J. *Synth. Commun.* **2007**, *37*, 3421.
- (666) Galabov, B.; Nalbantova, D.; Schleyer, P. V.; Schaefer, H. F. *Acc. Chem. Res.* **2016**, *49*, 1191.
- (667) Saikia, I.; Borah, A. J.; Phukan, P. *Chem. Rev.* **2016**, *116*, 6837.
- (668) Podgorsek, A.; Zupan, M.; Iskra, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 8424.
- (669) Iskra, J. *Top. Heterocycl. Chem.* **2012**, *27*, 269.
- (670) Podgorsek, A.; Stavber, S.; Zupan, M.; Iskra, J. *Green Chem.* **2007**, *9*, 1212.
- (671) Ganguly, N. C.; De, P.; Dutta, S. *Synthesis Stuttgart* **2005**, 1103.

References

- (672) Zhang, R.; Huang, L.; Zhang, Y. F.; Chen, X. R.; Xing, W. H.; Huang, J. *Catal. Lett.* **2012**, *142*, 378.
- (673) Djerassi, C. *Chem. Rev.* **1948**, *43*, 271.
- (674) Urch, C. J. *Comprehensive Organic Functional Group Transformations* **1995**, *2*, 605.
- (675) Wallquist, O.; Iqbal, A.; Pfenninger, J.; Rochat, A. C. *US Patent* **1989**, US4810802 A.
- (676) Zhang, J. S.; Chang, X.; Bowman, E. C.; Holt, C. J.; Lodewyk, M. W.; Miller, R. M.; Xia, G. M. *J. Org. Chem.* **2015**, *80*, 9292.
- (677) Zhou, Z. S.; He, X. H. *Synthesis Stuttgart* **2011**, 207.
- (678) Bayer, R. W.; Oreilly, E. J. *J. Org. Chem.* **1958**, *23*, 311.
- (679) Chaudhuri, S. K.; Roy, S.; Bhar, S. *Beilstein J. Org. Chem.* **2012**, *8*, 323.
- (680) Macharla, A. K.; Nappunni, R. C.; Marri, M. R.; Peraka, S.; Nama, N. *Tetrahedron Lett.* **2012**, *53*, 191.
- (681) Naresh, M.; Kumar, M. A.; Reddy, M. M.; Swamy, P.; Nanubolu, J. B.; Narender, N. *Synthesis Stuttgart* **2013**, *45*, 1497.
- (682) Adimurthy, S.; Ramachandraiah, G.; Bedekar, A. V.; Ghosh, S.; Ranu, B. C.; Ghosh, P. K. *Green Chem.* **2006**, *8*, 916.
- (683) Joshi, G.; Adimurthy, S. *Ind. Eng. Chem. Res.* **2011**, *50*, 12271.
- (684) Ryzhakov, A. V.; Nizhnik, Y. P.; Andreev, V. P. *Russ. J. Org. Chem.* **2000**, *36*, 884.
- (685) Ryzhakov, A. V.; Andreev, V. P.; Rodina, L. L. *Zh. Org. Khim.* **1996**, *32*, 128.
- (686) Kanibolotskii, A. L.; Mikhailov, V. A.; Savelova, V. A. *Zh. Org. Khim.* **1994**, *30*, 1053.
- (687) Ryzhakov, A. V.; Rodina, L. L. *Russ. J. Gen. Chem.* **2006**, *76*, 126.
- (688) Andreev, V. P.; Ryzhakov, A. V.; Morozov, A. K.; Alekseeva, O. O.; Rodina, L. L. *Khim. Geterotsikl. Soedin.* **1995**, 760.
- (689) Terao, J.; Nakamura, M.; Kambe, N. *Chem. Commun.* **2009**, 6011.
- (690) Paudler, W. W.; Jovanovic, M. V. *J. Org. Chem.* **1983**, *48*, 1064.
- (691) Bellucci, G.; Berti, G.; Bianchini, R.; Orsini, L. *Tetrahedron Lett.* **1982**, *23*, 3635.
- (692) Burwell, R. L.; Fuller, M. E. *J. Am. Chem. Soc.* **1957**, *79*, 2332.
- (693) Shibatomi, K.; Zhang, Y.; Yamamoto, H. *Chem. Asian. J.* **2008**, *3*, 1581.
- (694) Yesodharan, E. P.; Rajaram, J.; Kuriacose, J. C. *Int. J. Chem. Kinet.* **1976**, *8*, 277.
- (695) Wakeham, R. J.; Taylor, J. E.; Bull, S. D.; Morris, J. A.; Williams, J. M. J. *Org. Lett.* **2013**, *15*, 702.
- (696) Bruner, L. Z. *Phys. Chem.* **1902**, *41*, 514.
- (697) Kothandaraman, G.; Rajaram, J.; Kuriacose, J. C. *Proc. Indian Acad. Sci.* **1970**, *72*, 144.
- (698) Yeddanapalli, L. M.; Gnanapragasam, N. S. *J. Chem. Soc.* **1956**, 4934.
- (699) Joshi, S. B.; Vibhute, Y. B. *Asian J. Chem.* **1990**, *2*, 298.
- (700) Bamford, C. H.; Tipper, C. F. H. *Comprehensive Chemical Kinetics: Reactions of Aromatic Compounds*; Elsevier: Amsterdam, 1972.
- (701) Cooke, J. W. B.; Bright, R.; Coleman, M. J.; Jenkins, K. P. *Org. Process Res. Dev.* **2001**, *5*, 383.
- (702) Souza, F. E. S.; Sutherland, H. S.; Carlini, R.; Rodrigo, R. *J. Org. Chem.* **2002**, *67*, 6568.
- (703) Joshi, A. V.; Baidossi, M.; Mukhopadhyay, S.; Sasson, Y. *Org. Process Res. Dev.* **2004**, *8*, 568.

- (704) Gavara, L.; Boisse, T.; Rigo, B.; Henichart, J. P. *Tetrahedron* **2008**, *64*, 4999.
- (705) Datta, R. L.; Chatterjee, N. R. *J. Am. Chem. Soc.* **1916**, *38*, 2545.
- (706) Zhang, Y. H.; Shibatomi, K.; Yamamoto, H. *Synlett* **2005**, 2837.
- (707) Anderson, H. R.; Scheraga, H. A.; Vanartsdalen, E. R. *J. Chem. Phys.* **1953**, *21*, 1258.
- (708) Itoh, A.; Masaki, Y. *Synlett* **1997**, 1450.
- (709) Patil, R. D.; Bhadra, S.; Adimurthy, S.; Ranu, B. C. *Synth. Commun.* **2010**, *40*, 2922.
- (710) Nguyen, T. V.; Bekensir, A. *Org. Lett.* **2014**, *16*, 1720.
- (711) Xia, X. S.; Toy, P. H. *Beilstein J. Org. Chem.* **2014**, *10*, 1397.
- (712) Mirjafari, A.; Mohammadpoor-Baltork, I.; Moghadam, M.; Tangestaninejad, S.; Mirkhani, V.; Khosropour, A. R. *Tetrahedron Lett.* **2010**, *51*, 3274.
- (713) Cahiez, G.; Chaboche, C.; Mahuteau-Betzer, F.; Ahr, M. *Org. Lett.* **2005**, *7*, 1943.
- (714) Yang, C. T.; Zhang, Z. Q.; Liu, Y. C.; Liu, L. *Angew. Chem. Int. Ed.* **2011**, *50*, 3904.
- (715) Verwater, H. J. C.; Vanbeek, H. C. A. *Ind. Eng. Chem. Prod. Res. Dev.* **1986**, *25*, 631.
- (716) Vollhardt, P.; Schore, N. *Organic Chemistry: Structure and Function, Seventh Edition*; W. H. Freeman and Company: New York, USA, 2014.
- (717) Li, Y. J.; Ju, J.; Jia, J. H.; Sheng, W. J.; Han, L. A.; Gao, J. R. *Chin. J. Chem.* **2010**, *28*, 2428.
- (718) Choudary, B. M.; Someshwar, T.; Reddy, C. V.; Kantam, M. L.; Ratnam, K. J.; Sivaji, L. V. *Appl. Catal., A* **2003**, *251*, 397.
- (719) Li, X. F.; Li, L. C.; Tang, Y. F.; Zhong, L.; Cun, L. F.; Zhu, J.; Liao, J.; Deng, J. G. *J. Org. Chem.* **2010**, *75*, 2981.
- (720) Ma, L.; Jiao, P.; Zhang, Q.; Du, D.-M.; Xu, J. *Tetrahedron: Asymmetry* **2007**, *18*, 878.
- (721) Pedersen, E. B.; Carlsen, D. *Synthesis Stuttgart* **1978**, 844.
- (722) Shih, J. L.; Nguyen, T. S.; May, J. A. *Angew. Chem. Int. Ed.* **2015**, *54*, 9931.
- (723) Kerr, W. J.; Mudd, R. J.; Paterson, L. C.; Brown, J. A. *Chem. Eur. J.* **2014**, *20*, 14604.
- (724) Stern, T.; Rückbrod, S.; Czekelius, C.; Donner, C.; Brunner, H. *Adv. Synth. Catal.* **2010**, *352*, 1983.
- (725) Zhu, L.; Wang, W.; Huang, H.; Lin, Z.; Mou, L.; Nie, Z.; He, Y.; Ouyang, X.; Peng, S.; Zhang, D.; Wei, J. *European Patent Office* **2007**, EP1783115 A1.
- (726) Taylor, M. S.; Zalatan, D. N.; Lerchner, A. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 1313.
- (727) He, Y.; Shen, N. N.; Fan, X. S.; Zhang, X. Y. *Tetrahedron* **2013**, *69*, 8818.
- (728) Lin, Y. M.; Li, Z. T.; Casarotto, V.; Ehrmantraut, J.; Nguyen, A. N. *Tetrahedron Lett.* **2007**, *48*, 5531.
- (729) Edwards, M. L.; Ritter, H. W.; Stermerick, D. M.; Stewart, K. T. *J. Med. Chem.* **1983**, *26*, 431.
- (730) Braude, E. A.; Fawcett, J. S.; Newman, D. D. E. *J. Chem. Soc.* **1950**, 793.
- (731) Zhang, S. L.; Deng, Z. Q. *Org. Biomol. Chem.* **2016**, *14*, 7282.
- (732) Dhumaskar, K. L.; Bhat, C.; Tilve, S. G. *Synth. Commun.* **2014**, *44*, 1501.
- (733) Cabaleir, Mc; Chopra, A. B. *J. Chem. Soc., Perkin Trans. 2* **1974**, 452.
- (734) Tatsuzaki, J.; Bastow, K. F.; Nakagawa-Goto, K.; Nakamura, S.; Itokawa, H.; Lee, K. H. *J. Nat. Prod.* **2006**, *69*, 1445.

References

- (735) Dimmock, J. R.; Jha, A.; Kumar, P.; Zello, G. A.; Quail, J. W.; Oloo, E. O.; Oucharek, J. J.; Pasha, M. K.; Seitz, D.; Sharma, R. K.; Allen, T. M.; Santos, C. L.; Manavathu, E. K.; De Clercq, E.; Balzarini, J.; Stables, J. P. *Eur. J. Med. Chem.* **2002**, *37*, 35.
- (736) Bouziane, A.; Carboni, B.; Bruneau, C.; Carreaux, F.; Renaud, J.-L. *Tetrahedron* **2008**, *64*, 11745.
- (737) McConville, M.; Saidi, O.; Blacker, J.; Xiao, J. *J. Org. Chem.* **2009**, *74*, 2692.
- (738) Ma, S.; Liu, J.; Kuang, J.; Liu, Y.; Wang, Y.; Yu, Q.; Yuan, W.; Li, S.; Chen, B.; Cheng, J.; Wan, B.; Ye, J.; Yu, S. *US Patent* **2012**, US20120220792 A1.
- (739) Peach, P.; Cross, D. J.; Kenny, J. A.; Mann, I.; Houson, I.; Campbell, L.; Walsgrove, T.; Wills, M. *Tetrahedron* **2006**, *62*, 1864.
- (740) Braun, R. U.; Ansorge, M.; Muller, T. *J. Chem. Eur. J.* **2006**, *12*, 9081.
- (741) Sheshenev, A. E.; Boltukhina, E. V.; White, A. J. P.; Hii, K. K. *Angew. Chem. Int. Ed.* **2013**, *52*, 6988.
- (742) Ash, M. L.; Boykin, D. W.; Obrien, F. L. *J. Org. Chem.* **1972**, *37*, 106.
- (743) Aher, R. B.; Wanare, G.; Kawathekar, N.; Kumar, R. R.; Kaushik, N. K.; Sahal, D.; Chauhan, V. *S. Bioorg Med Chem Lett* **2011**, *21*, 3034.
- (744) Weber, W. M.; Hunsaker, L. A.; Abcouwer, S. F.; Deck, L. M.; Vander Jagt, D. L. *Bioorg. Med. Chem.* **2005**, *13*, 3811.
- (745) Arnold, A.; Markert, M.; Mahrwald, R. *Synthesis Stuttgart* **2006**, 1099.
- (746) Schmidt, B.; Elizarov, N.; Berger, R.; Holter, F. *Org. Biomol. Chem.* **2013**, *11*, 3674.
- (747) Yamakoshi, H.; Ohori, H.; Kudo, C.; Sato, A.; Kanoh, N.; Ishioka, C.; Shibata, H.; Iwabuchi, Y. *Bioorg. Med. Chem.* **2010**, *18*, 1083.
- (748) Shibata, H.; Iwabuchi, Y.; Ohori, H.; Yamakoshi, H.; Kakudo, Y. *US Patent* **2010**, US20100152493 A1.
- (749) Grant, T. N.; West, F. G. *J. Am. Chem. Soc.* **2006**, *128*, 9348.
- (750) Swislocka, R.; Kalinowska, M.; Ferenc, W.; Sarzynski, J.; Lewandowski, W. *Cent. Eur. J. Chem.* **2012**, *10*, 1095.
- (751) Monteiro, J.; de Bettencourt-Dias, A.; Mazali, I. O.; Sigoli, F. A. *New J. Chem.* **2015**, *39*, 1883.
- (752) Lindberg, B. J. *Acta Chem. Scand.* **1968**, *22*, 571.
- (753) Danno, S.; Moritani, I.; Fujiwara, Y. *Tetrahedron* **1969**, *25*, 4809.
- (754) Moloney, M. G.; Pinhey, J. T.; Stoermer, M. J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2645.
- (755) Yakawa, Y. *Memoirs of the Institute of Scientific and Industrial Research, Osaka University* **1952**, *9*, 180.
- (756) Ryan, S. J.; Candish, L.; Lupton, D. W. *J. Am. Chem. Soc.* **2009**, *131*, 14176.
- (757) Huang, F.; Quach, T. D.; Batey, R. A. *Org. Lett.* **2013**, *15*, 3150.
- (758) Nishiumi, M.; Miura, H.; Wada, K.; Hosokawa, S.; Inoue, M. *Adv. Synth. Catal.* **2010**, *352*, 3045.
- (759) Meng, L. K.; Kamada, Y.; Muto, K.; Yamaguchi, J.; Itami, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 10048.

- (760) Guzman, J. A.; Mendoza, V.; Garcia, E.; Garibay, C. F.; Olivares, L. Z.; Maldonado, L. A. *Synth. Commun.* **1995**, *25*, 2121.
- (761) Hight, R. J.; Hight, P. F. *J. Org. Chem.* **1965**, *30*, 902.
- (762) Kim, B. R.; Sung, G. H.; Ryu, K. E.; Yoon, H. J.; Lee, S.-G.; Yoon, Y.-J. *Synlett* **2014**, *25*, 1909.
- (763) Arisawa, M.; Igarashi, Y.; Kobayashi, H.; Yamada, T.; Bando, K.; Ichikawa, T.; Yamaguchi, M. *Tetrahedron* **2011**, *67*, 7846.
- (764) Sattenapally, N.; Wang, W.; Liu, H. M.; Gao, Y. *Tetrahedron Lett.* **2013**, *54*, 6665.
- (765) Yang, J. L.; Xu, F.; Shi, S. Q.; Nie, J. *Photochem. Photobiol. Sci.* **2012**, *11*, 1377.
- (766) Zhou, C.; Zeng, R.; Zou, J. *Chin. J. Chem.* **2010**, *28*, 294.
- (767) Jones, K. M.; Tomkinson, N. C. *J. Org. Chem.* **2012**, *77*, 921.
- (768) Picon, S.; Rawling, M.; Campbell, M.; Tomkinson, N. C. *Org. Lett.* **2012**, *14*, 6250.
- (769) Rumero, A.; Borreguero, I.; Sinisterra, J. V.; Alcantara, A. R. *Tetrahedron* **1999**, *55*, 14947.
- (770) Nammalwar, B.; Muddala, N. P.; Watts, F. M.; Bunce, R. A. *Tetrahedron* **2015**, *71*, 9101.
- (771) Sekiya, M.; Hara, A.; Ito, K.; Suzuki, J.; Tanaka, K. *Chem. Pharm. Bull.* **1967**, *15*, 774.
- (772) Kang, B.; Hong, S. H. *Adv. Synth. Catal.* **2015**, *357*, 834.
- (773) Fu, R. Z.; Yang, Y.; Chen, Z. K.; Lai, W. C.; Ma, Y. F.; Wang, Q.; Yuan, R. X. *Tetrahedron* **2014**, *70*, 9492.
- (774) Kitagawa, T.; Arita, J.; Nagahata, A. *Chem. Pharm. Bull.* **1994**, *42*, 1655.
- (775) Huang, G. Z.; Kling, B.; Darras, F. H.; Hellmann, J.; Decker, M. *Eur. J. Med. Chem.* **2014**, *81*, 15.
- (776) Gonzalez-Gomez, A.; Dominguez, G.; Perez-Castells, J. *Tetrahedron* **2009**, *65*, 3378.
- (777) Cheeseman, G. W. H. *J. Chem. Soc.* **1957**, 115.
- (778) Wolstenhulme, J. R.; Cavell, A.; Gredicak, M.; Driver, R. W.; Smith, M. D. *Chem. Commun.* **2014**, *50*, 13585.
- (779) Bakibayev, A. A.; Tignibidina, L. G.; Filimonov, V. D.; Pustovoitov, A. V.; Gorshkova, V. K.; Saratkov, A. S.; Krasnov, V. A. *Khim. Farm. Zh.* **1989**, *23*, 1455.
- (780) Kamer, P. C. J.; Nolte, R. J. M.; Drenth, W. *J. Am. Chem. Soc.* **1988**, *110*, 6818.
- (781) Shutske, G.; Harris, K. J.; Bordeau, K. J.; Angelastro, M. R.; John, S.; Klein, J. T.; Lu, J.; Bomont, C. *World Intellectual Property Organisation* **2005**, WO2005111025 A1.
- (782) Ke, Z. G.; Zhang, Y.; Cui, X. J.; Shi, F. *Green Chem.* **2016**, *18*, 808.
- (783) Okano, T.; Fujiwara, K.; Konishi, H.; Kiji, J. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 1975.
- (784) Borel, C.; Hegedus, L. S.; Krebs, J.; Satoh, Y. *J. Am. Chem. Soc.* **1987**, *109*, 1101.
- (785) Itsenko, O.; Blom, E.; Långström, B.; Kihlberg, T. *Eur. J. Org. Chem.* **2007**, *2007*, 4337.
- (786) Habibi, D.; Nasrollahzadeh, M. *C. R. Chim.* **2013**, *16*, 1008.
- (787) Lanigan, R. M.; Starkov, P.; Sheppard, T. D. *J. Org. Chem.* **2013**, *78*, 4512.
- (788) Fu, R. Z.; Yang, Y.; Ma, Y. S.; Yang, F.; Li, J. J.; Chai, W.; Wang, Q.; Yuan, R. X. *Tetrahedron Lett.* **2015**, *56*, 4527.
- (789) Bencivenni, G.; Lanza, T.; Leardini, R.; Minozzi, M.; Nanni, D.; Spagnolo, P.; Zanardi, G. *J. Org. Chem.* **2008**, *73*, 4721.
- (790) Janza, B.; Studer, A. *Org. Lett.* **2006**, *8*, 1875.

References

- (791) Wei, Y. W.; Wu, J. J.; Xue, D.; Wang, C.; Liu, Z. T.; Zhang, Z. Z.; Chen, G. F.; Xiao, J. L. *Synlett* **2014**, 25, 1295.
- (792) Zhang, C.; Xu, Z. J.; Shen, T.; Wu, G. L.; Zhang, L. R.; Jiao, N. *Org. Lett.* **2012**, 14, 2362.
- (793) Wang, Z.-G.; Lu, M. *RSC Adv.* **2014**, 4, 1234.
- (794) Pratap, T. V.; Baskaran, S. *Tetrahedron Lett.* **2001**, 42, 1983.
- (795) Pace, V.; de la Vega-Hernandez, K.; Urban, E.; Langer, T. *Org. Lett.* **2016**, 18, 2750.
- (796) Srinivas, P.; Likhari, P. R.; Maheswaran, H.; Sridhar, B.; Ravikumar, K.; Kantam, M. L. *Chem. Eur. J.* **2009**, 15, 1578.
- (797) Aitali, M.; Allaoud, S.; Karim, A.; Meliet, C.; Mortreux, A. *Tetrahedron: Asymmetry* **2000**, 11, 1367.
- (798) Guirado, A.; Zapata, A.; Gomez, J. L.; Trbalon, L.; Galvez, J. *Tetrahedron* **1999**, 55, 9631.